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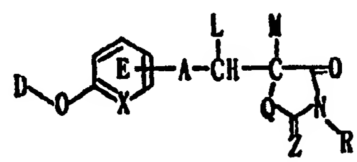
(54) Title: HETEROCYCLIC COMPOUNDS, THEIR PRODUCTION AND USE

(57) Abstract



(I)

A heterocyclic compound represented by formula (I), wherein D stands for H or an optionally substituted hydrocarbon group; X stands for CH or N; A stands for a divalent aliphatic hydrocarbon group; R stands for an optionally substituted hydrocarbon group; Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl), O or S; Z stands for O or S; L and M independently stand for H, or they may optionally be combined with each other to form a bond; ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring; or a salt thereof; which is useful as an antitumor agent.

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DESCRIPTION

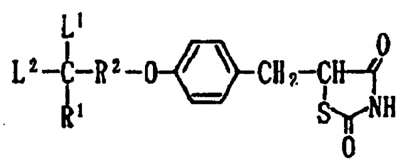
HETEROCYCLIC COMPOUNDS, THEIR PRODUCTION AND USE

TECHNICAL FIELD

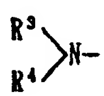
This invention relates to a novel heterocyclic compound useful as a medicine especially an antitumor agent, a method of producing it and a preparation comprising it.

BACKGROUND ART

In JPA S55(1980)-22636 (EP-A 8203), thiazolidine derivatives represented by the formula:



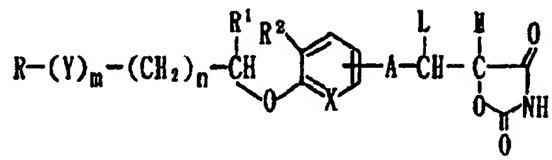
wherein R^1 stands for an alkyl group, a cycloalkyl group, a phenylalkyl group, phenyl group, a 5- or 6-membered heterocyclic group having one or two hetero-atoms selected from nitrogen atom, oxygen atom and sulfur atom, or a group represented by the formula:



wherein R^3 and R^4 independently stand for a lower alkyl group or R^3 and R^4 are combined with each other directly or through a hetero-atom selected from nitrogen atom, oxygen atom and sulfur atom to optionally form a 5- or 6-membered ring, taken together with the nitrogen atom adjacent to R^3 and R^4;
R^2 stands for a bond or a lower alkylene group;
L^1 and L^2 independently stand for, when R^1 is an alkyl group, a lower alkyl group, or they may optionally be combined with each other to form an alkylene group,

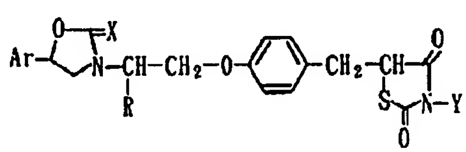
and, when R^1 is not an alkyl group, L^1 and L^2 may, besides the above definition, optionally be hydrogen atom; are described, and there is also disclosed that these compounds have an activity of lowering lipid in blood and sugar in blood.

In JPA H7(1995)-165735 (EP-A 612743), 2,4-oxazolidine derivatives represented by the formula:



wherein R stands for an optionally substituted hydrocarbon residue, or heterocyclic group; Y stands for a group shown by -CO-, -CH(OH)- or NR^3- (wherein R^3 stands for an optionally substituted alkyl group); m denotes 0 or 1; n denotes 0, 1 or 2; X stands for CH or N; A stands for a C_{1-7} divalent aliphatic hydrocarbon residue; R^1 and R^2 independently stand for hydrogen atom or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M respectively stand for hydrogen atom, or L and M may optionally be combined with each other to form a bond; and their salts as well as their use as a therapeutic agent of diabetes mellitus are disclosed.

In JPA H6(1994)-157522 (EP-A 590793), there is disclosed that thiazolidine derivatives represented by the formula:



wherein R stands for a C_{1-8} straight-chain or branched alkyl group; X stands for oxygen atom or sulfur atom; Y

stands for hydrogen atom or a group: -A-COOH (A stands for a C_{1-6} straight chain or branched alkylene group); Ar stands for a C_{6-10} aryl group optionally having the same or different one to five substituents (a), and the said substituents (a) include halogen, haloalkyl having C_{1-4} straight-chain or branched alkyl, hydroxy, C_{1-4} straight-chain or branched alkyl or C_{1-4} straight-chain or branched alkoxy; are useful as prophylactic and/or therapeutic agents of, among others, hyperglycemia, hyperlipemia and obesity.

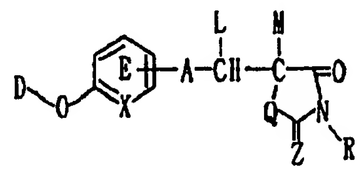
However, use of these azolidine compounds as antitumor agent has not been known.

So far, the study of antitumor agents has been conducted broadly, and antitumor agents having less side-effects and being of a high practical value are desired. For example, even in the case of early breast cancer in which no metastatis is observed, in spite of ardent study on adjuvant chemotherapy by combination of known antitumor agents, the therapeutic effects are only temporary and no radical cure of the patient has been observed while involving a risk of side-effects and secondary carcinogenesis caused by a drug. Further, it is considered that adjuvant therapy is not applicable to patients with invasive progressive breast cancer [c.f.: e.g. "Adjuvant Therapy for Node-Negative Breast Cancer", Section 11 of "Important Advances in Oncology 1990" Edited by DeVita, Hellman and Rosenberg, Published by J. B. Lippincott Company (Philadelphia) 1990, p.183]. Therefore, development of antitumor agents which suppress cancer cells selectively and are based on a novel action mechanism is awaited.

The object of this invention is to provide such a novel antitumor agent having less side-effects and based on a novel action mechanism.

DISCLOSURE OF INVENTION

As a result of various studies for accomplishing the above-mentioned object, the present inventors succeeded in synthesizing, for the first time, a heterocyclic compound [hereinafter simply called "compound (I)"], whose characteristic feature on the chemical structure lies in that the 3-position of the azolidine is substituted and the 5-position is substituted with a side chain via two or more carbon atoms, which is represented by the formula (I):

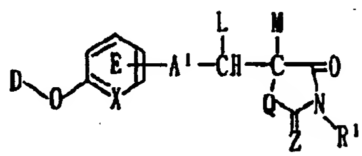


(I)

wherein D stands for hydrogen atom or an optionally substituted hydrocarbon group;
X stands for CH or N;
A stands for a divalent aliphatic hydrocarbon group;
R stands for a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;
Z stands for oxygen atom or sulfur atom;
L and M independently stand for hydrogen atom, or they may optionally be combined with each other to form one bond; and
ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring; or a salt thereof, and found that this compound (I) has, unexpectedly, an excellent suppressing action

of tyrosine kinase based on the specific chemical structure and can be safely used as an antitumor agent. Based on these finding, the present invention has been accomplished.

More specifically, the present invention relates to: (1) the compound (I) or a salt thereof;
(2) a pharmaceutical composition comprising the compound (I) or a salt thereof;
(3) an antitumor agent comprising a compound of the formula:



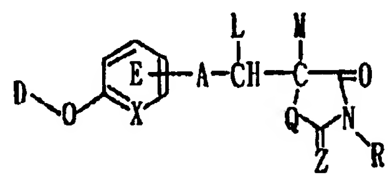
(II)

wherein D stands for hydrogen atom or an optionally substituted hydrocarbon group;
X stands for CH or N;
A^1 stands for a bond or a divalent aliphatic hydrocarbon group;
R^1 stands for hydrogen atom or a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;
Z stands for oxygen atom or sulfur atom;
L and M independently stand for hydrogen atom, or they may optionally be combined with each other to form one

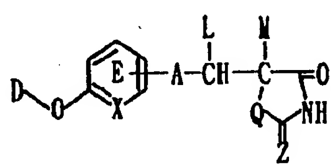
bond; and ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring; and when A^1 stands for a bond, D stands for an optionally substituted hydrocarbon group; or a salt thereof;

(4) a tyrosine kinase inhibitor which comprises the compound (II) or a salt thereof;

(5) a method of producing a compound represented by the formula:



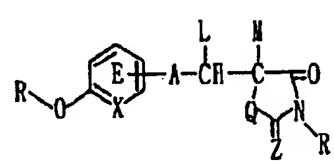
wherein symbols are of the same meaning as defined above, or a salt thereof, which is characterized by allowing a compound represented by the formula:



wherein symbols are of the same meaning as defined above, or a salt thereof to react with a compound represented by the formula: R-W

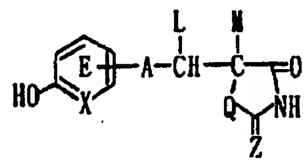
wherein W stands for a leaving group and R is of the same meaning as defined above, or a salt thereof; and

(6) a method of producing a compound represented by the formula:



wherein symbols are of the same meaning as defined

above, or a salt thereof, which is characterized by allowing a compound represented by the formula:



wherein symbols are of the same meaning as defined above, or a salt thereof to react with a compound represented by the formula: R-W

wherein W stands for a leaving group and R is of the same meaning as defined above, or a salt thereof.

In the above formulae, D stands for hydrogen atom or an optionally substituted hydrocarbon group.

As the hydrocarbon group shown by D, mention is made of, for example, aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, aromatic hydrocarbon groups, aromatic-aliphatic hydrocarbon groups and alicyclic-aliphatic hydrocarbon groups.

As the aliphatic hydrocarbon groups, use is made of, for example, C_{1-10} aliphatic hydrocarbon groups. Examples of the aliphatic hydrocarbon groups include C_{1-10}, preferably C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, heptyl, octyl, and decyl; and C_{2-10}, preferably C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) such as vinyl (ethenyl), 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-

pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and geranyl.

As the alicyclic hydrocarbon groups, use is made of, for example, C_{3-7} alicyclic hydrocarbon groups. Examples of the alicyclic hydrocarbon groups include C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, and 2,4-cycloheptadienyl.

As the aromatic hydrocarbon groups, mention is made of, for example, C_{6-14} aromatic hydrocarbon groups. Examples of the aromatic hydrocarbon groups include C_{6-14} aryl groups such as phenyl and naphthyl (α-naphthyl, β-naphthyl).

As the aromatic-aliphatic hydrocarbon groups, mention is made of, for example, C_{7-20} aromatic-aliphatic hydrocarbon groups. Examples of the aromatic-aliphatic hydrocarbon groups include C_{7-14} aralkyl groups (e.g. benzyl, 2-phenylethyl) and C_{6-14} aryl-C_{2-6} alkenyl groups (e.g. styryl(2-phenylethenyl), 2-(2-naphthyl)vinyl, 4-phenyl-1,3-butadienyl).

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups, C_{4-9} ones. Examples of the alicyclic-aliphatic hydrocarbon groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl,

and cycloheptylethyl.

The hydrocarbon group shown by D is preferably an aliphatic hydrocarbon group, more preferably a C_{1-6} aliphatic hydrocarbon group.

The hydrocarbon group shown by D may optionally have, at any possible position, 1 to 4 substituents selected from, for example, "an optionally substituted heterocyclic group", "an aliphatic chain hydrocarbon group", "an alicyclic hydrocarbon group", "an optionally substituted aromatic hydrocarbon group", "an aromatic-aliphatic hydrocarbon group", "a halogen atom", "nitro group", "an optionally substituted amino group", "an optionally substituted acyl group", "an optionally substituted hydroxyl group", "an optionally substituted thiol group", "an optionally esterified carboxyl group", "cyano group" and "oxo group".

The heterocyclic group in "the optionally substituted heterocyclic group" as the substituent of the hydrocarbon group shown by D includes, for example, 5- to 7-membered heterocyclic groups containing in addition to carbon atom, as a ring component atom, 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and condensed ring groups. Examples of the 5- to 7-membered heterocyclic groups include a 5- to 7-membered heterocyclic group containing one sulfur atom, nitrogen atom or oxygen atom, a 5- to 6-membered heterocyclic group containing two to four nitrogen atoms and a 5- to 6-membered heterocyclic group containing one or two nitrogen atoms and one sulfur atom or oxygen atom.

Examples of the condensed ring groups include, for example, those formed by condensation of the above-mentioned 5- to 7-membered heterocyclic groups with a 6-membered ring containing two or less nitrogen atom, benzene ring or a 5-membered ring containing one sulfur atom. Specific examples of these heterocyclic groups

include pyran, dihydropyran, tetrahydropyran, chroman, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,3,4-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, benzpyrazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl, furyl, thienyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl. Among these, oxazolyl, thiazolyl and triazolyl are preferable, and oxazolyl or thiazolyl is more preferable.

Examples of "the aliphatic chain hydrocarbon group" as the substituent of the hydrocarbon group shown by D include C_{1-15} straight-chain or branched

aliphatic hydrocarbon groups as exemplified by alkyl groups, alkenyl groups, and alkynyl groups.

Preferable examples of the alkyl groups include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl groups include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl. Preferable examples of the alkynyl groups include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

Examples of "the alicyclic hydrocarbon group" as the substituent of the hydrocarbon group shown by D include C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups, for example, cycloalkyl groups, cycloalkenyl groups and cycloalkadienyl groups.

Preferable examples of the cycloalkyl groups include C_{3-12} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl groups include C_{5-12} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-

cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl groups include C_{5-12} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

The aromatic hydrocarbon group in "the optionally substituted aromatic hydrocarbon group" as the substituent of the hydrocarbon group shown by D means monocyclic or condensed polycyclic aromatic hydrocarbon group. Preferable examples of the aromatic hydrocarbon group include C_{6-14} aromatic hydrocarbon groups such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and 3,4-dihydro-2-naphthyl. Among them, phenyl, 1-naphthyl and 2-naphthyl are preferable.

Examples of substituents in "the optionally substituted aromatic hydrocarbon group" as the substituent of the hydrocarbon group shown by D include halogen (e.g. fluorine, chlorine, bromine and iodine), a lower alkyl group (e.g. C_{1-6} alkyl groups such as methyl, ethyl, propyl and butyl), a lower alkoxy group (e.g. C_{1-6} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentyloxy), hydroxyl group, nitro group, cyano group, an acyl group (e.g. C_{1-6} alkanoyl groups such as formyl, acetyl, propionyl and butyryl), amino group, thiol group and trifluoromethyl group. The number of substituents is, for example, one to five.

Examples of "the aromatic-aliphatic hydrocarbon group" as the substituent of the hydrocarbon group shown by D include C_{7-20} aromatic-aliphatic hydrocarbon groups. Examples of the aromatic-aliphatic hydrocarbon groups include C_{7-14} aralkyl groups (e.g. benzyl, 2-phenylethyl), C_{6-14} aryl-C_{2-6} alkenyl groups (e.g. styryl(2-phenylethenyl), 2-(2-naphthyl)vinyl, 4-phenyl-1,3-butadienyl).

Examples of "the halogen atom" as the substituent

of the hydrocarbon group shown by D include fluorine, chlorine, bromine and iodine, and, among them, fluorine and chlorine are especially preferable.

Examples of "the optionally substituted amino group" as the substituent of the hydrocarbon group shown by D include, amino group which is mono- or di-substituted by C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} acyl or aromatic group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, acetylamino, propionylamino, benzoylamino, phenylamino and N-methyl-N-phenylamino) and a 4- to 6-membered cyclic amino group (e.g. 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino and 1-piperazinyl). The 4- to 6-membered cyclic amino group may optionally be further substituted by 1) C_{1-6} alkyl groups, 2) C_{6-14} aryl groups optionally substituted by halogen, C_{1-6} alkoxy groups or trifluoromethyl, 3) 5- or 6-membered heterocyclic groups containing in addition to carbon atom, as a ring component atom, 1 or 2 nitrogen atoms (e.g. 2-pyridyl, pyrimidinyl), or 4) 6-membered cyclic amino group (e.g. piperidino, 1-piperadinyl).

As the acyl group in "the optionally substituted acyl group" as the substituent of the hydrocarbon group shown by D, mention is made of, besides formyl, for example, groups formed by combination of C_{1-10} alkyl, C_{2-10} alkenyl or C_{6-12} aromatic group with carbonyl group (e.g. acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl and nicotinoyl).

As substituents in "the optionally substituted acyl group", mention is made of, for example, C_{1-3} alkyl groups, C_{1-3} alkoxy groups, halogen (e.g. chlorine, fluorine or bromine), nitro group, hydroxyl group and

amino group. The number of substituents is, for example, 1 to 3.

As the substituted hydroxyl group in "the optionally substituted hydroxyl group" as the substituent of the hydrocarbon group shown by D , mention is made of, for example, hydroxyl group which is substituted by hydrocarbon groups or acyl groups, such as alkoxy groups , alkenyloxy groups, aralkyloxy groups, aryloxy groups and acyloxy groups. Preferable examples of the alkoxy groups include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy groups include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy and 2-cyclohexenylmethoxy. Preferable examples of the aralkyloxy groups include phenyl-C_{1-4} alkyloxy groups (e.g. benzyloxy, phenethyloxy).

Preferable examples of the aryloxy groups include C_{6-14} aryloxy groups such as phenoxy and 4-chlorophenoxy.

Preferable examples of the acyloxy groups include C_{2-4} acyloxy groups such as C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy, isobutyryloxy).

As the substituted thiol group in "the optionally substituted thiol group" as the substituent of the hydrocarbon group shown by D, mention is made of, thiol group which is substituted by hydrocarbon groups or acyl groups, such as alkylthio groups, alkenylthio groups, aralkylthio groups, arylthio groups and acylthio groups. Preferable examples of the alkylthio groups include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio,

butylthio, isobutylthio, sec.-butylthio, tert.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio groups include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio, 2-cyclopentenylmethylthio and 2-cyclohexenylmethylthio. Preferable examples of the aralkylthio groups include C_{7-14} aralkylthio groups such as phenyl-C_{1-4} alkylthio (e.g. benzylthio, phenethylthio). Preferable examples of the arylthio groups include C_{6-14} arylthio groups such as phenylthio and 4-chlorophenylthio. Preferable examples of the acylthio groups include C_{2-4} acylthio groups such as C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio, isobutyrylthio).

As the esterified carboxyl group in "the optionally esterified carboxyl group" as the substituent of the hydrocarbon group shown by D, mention is made of, for example, alkoxycarbonyl groups, aralkyloxycarbonyl groups and aryloxycarbonyl groups. Preferable examples of the alkoxycarbonyl groups include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl groups include C_{8-15} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl groups include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

The heterocyclic groups as the substituent of the hydrocarbon group shown by D may optionally have at any possible position, one to three substituents, respectively. As these substituents, mention is made of "aliphatic chain hydrocarbon groups", "alicyclic hydrocarbon groups", "optionally substituted aromatic

hydrocarbon groups", "aromatic-aliphatic hydrocarbon groups", "aromatic heterocyclic groups", "non-aromatic heterocyclic groups", "halogen atoms", "nitro group", "optionally substituted amino groups", "optionally substituted acyl groups", "optionally substituted hydroxyl groups", "optionally substituted thiol groups", "optionally esterified carboxyl groups" and "aromatic heterocyclic-aliphatic hydrocarbon groups".

As these "aliphatic chain hydrocarbon groups", "alicyclic hydrocarbon groups", "aromatic hydrocarbon groups", "aromatic-aliphatic hydrocarbon groups", "halogen atoms", "optionally substituted amino groups", "optionally substituted acyl groups", "optionally substituted hydroxyl groups", "optionally substituted thiol groups" and "optionally esterified carboxyl groups", mention is made of similar ones to substituents of the hydrocarbon group shown by D. Preferable examples of "the aromatic heterocyclic groups" as substituents of the heterocyclic groups include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl,

phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of "the non-aromatic heterocyclic groups" as substituents of the heterocyclic groups include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl.

Preferable examples of "the aromatic heterocyclic-aliphatic hydrocarbon groups" as substituents of the heterocyclic groups include 2-furyl-C_{1-6} alkyl groups (e.g. (2-furyl)methyl), 2-furyl-C_{2-6} alkenyl groups (e.g. (2-furyl)vinyl), thienyl-C_{1-6} alkyl groups (e.g. thienylmethyl), thienyl-C_{2-6} alkenyl groups (e.g. 2-thienylvinyl).

Among the above-mentioned substituents, especially preferable ones on the heterocyclic groups as the substituent of the hydrocarbon group shown by D include styryl, phenyl, naphthyl, furyl, thienyl, C_{2-4} alkenyl groups and C_{1-6} alkyl groups.

D is preferably a hydrocarbon group which is substituted by an optionally substituted heterocyclic group, more preferably a hydrocarbon group which is substituted by oxazolyl or thiazolyl group optionally having one or two substituents selected from C_{1-6} alkyl groups, C_{2-8} alkenyl groups, C_{3-8} cycloalkyl groups, C_{6-14} aryl groups, C_{7-14} aralkyl groups, C_{6-14} aryl-C_{2-6} alkenyl groups, aromatic heterocyclic groups, aromatic heterocyclic-C_{1-6} alkyl groups and aromatic heterocyclic-C_{2-6} alkenyl groups.

Examples of the hydrocarbon group shown by R or R^1 include similar hydrocarbon group to those set forth as

D.

As the substituent of the hydrocarbon group shown by R or R^1, mention is made of, for example, (1) "an optionally substituted heterocyclic group", (2) "a halogen atom", (3) "nitro group", (4) "an optionally substituted amino group", (5) "an optionally substituted acyl group", (6) "hydroxyl group optionally substituted by a hydrocarbon group or an acyl group", (7) "thiol group optionally substituted by a hydrocarbon group or an acyl group", (8) "an optionally esterified carboxyl group", (9) "cyano group" and (10) "oxo group". The number of substituents is, for example, one to four. Examples of these substituents include similar ones to those set forth as the substituent of the hydrocarbon group shown by D. The substituent of the optionally substituted hydrocarbon group shown by R or R^1 is preferably "an optionally substituted heterocyclic group", "a halogen atom", "nitro group", "an optionally substituted amino group", "an optionally substituted acyl group", "an optionally esterified carboxyl group", "cyano group" or "oxo group", more preferably "an optionally substituted heterocyclic group" or "an optionally substituted amino group". As the heterocyclic group in "the optionally substituted heterocyclic group", oxazolyl or thiazolyl is preferable. Preferable examples of substituents in "the optionally substituted heterocyclic group" include C_{1-6} alkyl groups (e.g. methyl, ethyl, propyl), C_{2-8} alkenyl groups (e.g. ethenyl, 1-propenyl, 2-propenyl, 1-butenyl), C_{3-8} cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-14} aryl groups (e.g. phenyl, naphthyl, anthryl), C_{7-14} aralkyl groups (e.g. benzyl, 2-phenylethyl), C_{6-14} aryl-C_{2-6} alkenyl groups (e.g. styryl(2-phenylethenyl), 2-(2-naphthyl)vinyl, 4-phenyl-1,3-butadienyl), aromatic heterocyclic groups (e.g. furyl,thienyl), aromatic

heterocyclic-C_{1-6} alkyl groups (e.g. (2-furyl)methyl), aromatic heterocyclic-C_{2-6} alkenyl groups (e.g. 2-(2-furyl)vinyl).

Preferable examples of the substituted amino groups in "the optionally substituted amino group" include C_{1-10} acylamino groups (e.g. C_{1-10} alkanoylamino such as acetylamino and propionylamino); mono- or di-C_{1-10} alkylamino groups (e.g. methylamino, ethylamino, dimethylamino, diethylamino); and 4- to 6-membered cyclic amino groups optionally substituted by 1) C_{1-6} alkyl groups, 2) C_{6-14} aryl groups optionally substituted by halogen, C_{1-6} alkoxy groups or trifluoromethyl, 3) 5- or 6-membered heterocyclic groups containing in addition to carbon atoms, as a ring component atom, 1 or 2 nitrogen atoms (e.g. 2-pyridyl, pyrimidinyl) or 4) 6-membered cyclic amino groups (e.g. piperidino, 1-piperadinyl), (e.g. 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, 4-piperidino-1-piperidinyl, 4-(3-chlorophenyl)piperadinyl, 4-methylpiperadinyl, 4-phenylpiperadinyl, 4-(4-fluorophenyl)piperadinyl, 4-(4-methoxyphenyl)piperadinyl, 4-(2-pyridyl)piperadinyl, 4-(pyrimidinyl)piperadinyl, 4-(4-trifluoromethylphenyl)piperadinyl. "The optionally substituted amino group" is preferably a 4- to 6-membered cyclic amino group optionally substituted by 1) C_{1-6} alkyl groups, 2) C_{6-14} aryl groups optionally substituted by halogen, C_{1-6} alkoxy groups or trifluoromethyl, 3) 5- or 6-membered heterocyclic groups containing in addition to carbon atoms, as a ring component atom, 1 or 2 nitrogen atoms or 4) 6-membered cyclic amino groups.

R^1 stands for hydrogen atom or a hydrocarbon group optionally having substituents selected from (1) "an optionally substituted heterocyclic group", (2) "a halogen atom", (3) "nitro group", (4) "an optionally

substituted amino group", (5) "an optionally substituted acyl group", (6) "hydroxyl group optionally substituted by a hydrocarbon group or an acyl group", (7) "thiol group optionally substituted by a hydrocarbon group or an acyl group", (8) "an optionally esterified carboxyl group", (9) "cyano group" and (10) "oxo group". R^1 preferably stands for a hydrocarbon group optionally having substituents selected from (1) to (10).

R and R^1 are preferably hydrocarbon groups substituted by 1) an optionally substituted heterocyclic group or 2) an optionally substituted amino group.

R and R^1 are more preferably hydrocarbon groups substituted by (a) oxazolyl or thiazolyl group optionally having 1 or 2 substituents selected from C_{1-6} alkyl groups, C_{2-8} alkenyl groups, C_{3-8} cycloalkyl groups, C_{6-14} aryl groups, C_{7-14} aralkyl groups, C_{6-14} aryl-C_{2-6} alkenyl groups, aromatic heterocyclic groups, aromatic heterocyclic-C_{1-6} alkyl groups, and aromatic heterocyclic-C_{2-6} alkenyl groups; or (b) 4- to 6-membered cyclic amino groups optionally substituted by 1) C_{1-6} alkyl groups, 2) C_{6-14} aryl groups optionally substituted by halogen, C_{1-6} alkoxy groups or trifluoromethyl, 3) 5- or 6-membered heterocyclic groups containing in addition to carbon atoms, as a ring component atom, 1 or 2 nitrogen atoms or 4) 6-membered cyclic amino groups.

As the divalent aliphatic hydrocarbon group shown by A or A^1, one having 1 to 7 carbon atoms is preferable, which may be straight-chain or branched, and may be saturated or unsaturated. Examples of the divalent aliphatic hydrocarbon group include saturated one such as $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_2-$, $-CH(C_2H_5)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$ and $-(CH_2)_7-$, and,

unsaturated one such as -CH=CH-, -C(CH_3)=CH-, -CH=CH-CH_2-, -C(C_2H_5)=CH-, -CH_2-CH=CH-CH_2-, -CH_2-CH_2-CH=CH-CH_2-, -CH=CH-CH=CH-CH_2-, and -CH=CH-CH=CH-CH=CH-CH_2-. A or A^1 is more preferably a C_{1-4} divalent aliphatic hydrocarbon group, with prefence given to saturated one. A or A^1 is especially preferably -CH_2- or -$(CH_2)_2$-.

X stands for CH or N, preferably CH.

Q stands for -N(R^0)- (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom, preferably oxygen atom. Examples of the lower alkyl group shown by R^0 include C_{1-4} one such as methyl, ethyl, propyl and butyl.

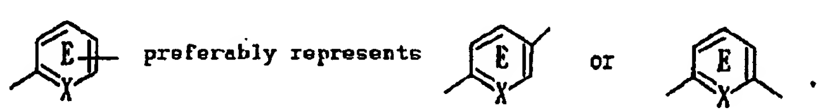
Z stands for oxygen atom or sulfur atom, preferably oxygen atom.

L and M are preferably hydrogen.

In the compounds of this invention, when L and M are combined with each other to form one bond, there exist (E) and (Z) isomers relative to the double bond at the 5-position of azolidine ring.

When L and M respectively stand for hydrogen atom, there exist optical isomers of (R) and (S) isomers due to the asymmetric carbon at the 5-position of azolidine ring.

In the compounds of this invention, the partial formula:



D includes groups shown by, for example, R^3-$(Y)_m$-$(CH_2)_n$-CH(D^1) wherein R^3 stands for an optionally substituted hydrocarbon group; m is 0 or 1; n is 0, 1 or 2; Y stands for -CO-, -CH(OH)- or -N(R^4) (R^4 stands for an optionally substituted alkyl group); D^1 stands for hydrogen atom or a lower alkyl group. As the

optionally substituted hydrocarbon groups shown by R^3, mention is made of ones similar to hydrocarbon groups set forth as D.

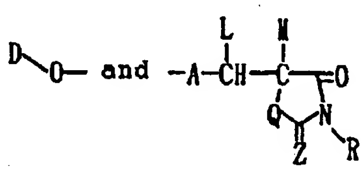
The symbol m denotes 0 or 1, preferably 0.

The symbol n denotes 0, 1 or 2, preferably 0 or 1, most preferably 0.

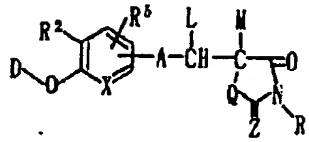
Y stands for -CO-, -CH(OH)- or -N(R^4)-, preferably -CH(OH)- or -N(R^4)-.

As the alkyl group in "the optionally substituted alkyl group" shown by R^4, mention is made of C_{1-4} one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl. Eamples of substituents in "the optionally substituted alkyl group" include halogen (e.g. fluorine, chlorine, bromine, iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy and tert.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. alkanoyl groups such as formyl, acetyl and propionyl).

Ring E may optionally have, besides



, one to four substituents selected from a lower (C_{1-4}) alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl), a lower (C_{1-4}) alkoxy group (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy and tert.-butoxy), halogen (e.g. fluorine, chlorine, bromine and iodine), amino group, nitro group and hydroxyl group. Especially, as examples of compounds in which ring E is further substituted, mention is made of compounds represented by the formula:



(I-a)

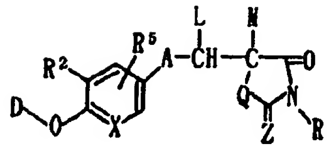
wherein R^2 and R^5 independently stand for hydrogen atom, a lower alkyl group, a lower alkoxy group, a halogen atom or hydroxyl group, or, R^2 and D may optionally be combined with each other to form a 5- or 6-membered heterocyclic ring optionally containing nitrogen atom or oxygen atom, and other symbols are of the same meaning as defined above, or their salts.

As the lower alkyl group shown by R^2 and R^5, mention is made of C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl.

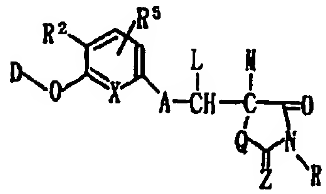
As the lower alkoxy group shown by R^2 and R^5, mention is made of a C_{1-4} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy and tert.-butoxy.

As the halogen atom shown by R^2 and R^5, mention is made of fluorine, chloride, bromine and iodine, preferably fluorine or chlorine.

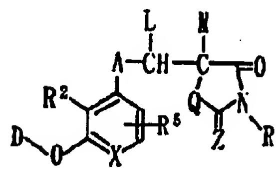
Especially, the compounds represented by the formula (I-a) include those represented by the following formulae.



(I-a-1)



(I-a-2)

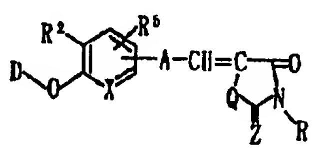


(I-a-3)

wherein each symbol is of the same meaning as defined above.

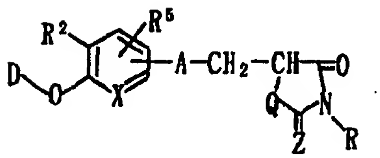
When medicinal effects and toxicity are taken into consideration, among compounds represented by the formulae (I-a-1), (I-a-2) and (I-a-3), those represented by (I-a-1) and (I-a-2) are preferable, and, those represented by (I-a-1) are most preferable.

The compounds wherein L and M are combined with each other to form one bond in the formula (I-a), are represented by the formula:



(I-b-1)

wherein each symbol is of the same meaning as defined above, and, the compounds wherein L and M respectively stand for hydrogen atom are represented by the formula:



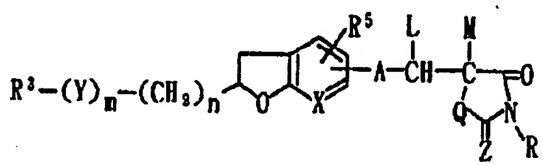
(I-b-2)

wherein each symbol is of the same meaning as defined above.

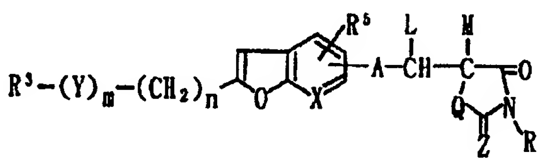
Among compounds represented by the formulae (I-b-1) and (I-b-2), the compound represented by the formula (I-b-2) is preferable.

Examples of the compounds wherein substituents in ring E (R^2) are combined with D to form a ring (e.g. a 5- or 6-membered heterocyclic ring optionally containing nitrogen atom) in the formula (I), include the compounds represented by the following formulae.

(1) D and R^2 are combined with each other to form a 5-membered heterocyclic ring.

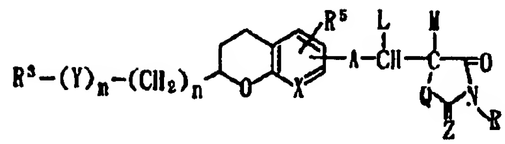


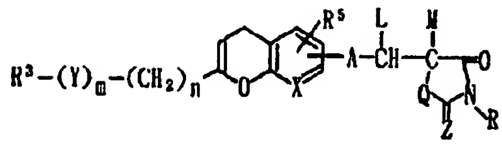
(I-c-1)

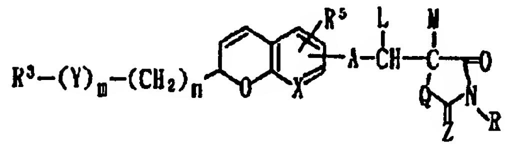


(I-c-2)

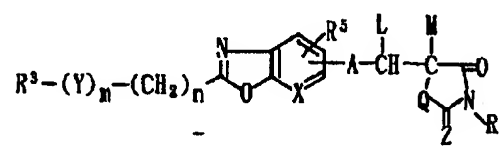
(2) D and R^2 are combined with each other to form a 6-membered heterocyclic ring.


(I-c-3)

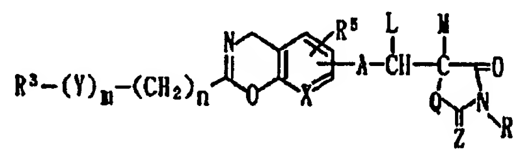

(I-c-4)

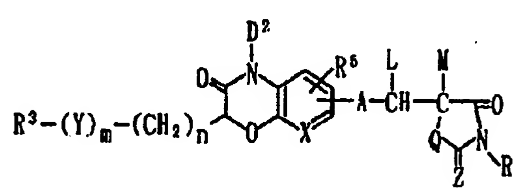

(I-c-5)

(3) D and R^2 are combined with each other to form a 5-membered heterocyclic ring containing a nitrogen atom.


(I-c-6)

(4) D and R^2 are combined with each other to form a 6-membered heterocyclic ring containing a nitrogen atom.


(I-c-7)


(I-c-8)

wherein D^2 stands for hydrogen atom or a lower alkyl group, and other symbols are of the same meaning as defined above.

The lower alkyl group shown by D^2 is exemplified by C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, sec.-butyl and tert.-butyl.

Among the compounds represented by the formulae (I-c-1) to (I-c-8), compounds represented by the formulae (I-c-2), (I-c-3) and (I-c-6) are preferable.

Preferable examples of the compound represented by the formula (I) or (II) include compounds wherein D is C_{1-6} aliphatic hydrocarbon groups substituted by oxazolyl or thiazolyl group optionally having one or two substituents selected from C_{1-6} alkyl groups, C_{2-8} alkenyl groups, C_{3-8} cycloalkyl groups, C_{6-14} aryl groups, C_{7-14} aralkyl groups, C_{6-14} aryl-C_{2-6} alkenyl groups, aromatic heterocyclic groups, aromatic heterocyclic-C_{1-6} alkyl groups, and aromatic heterocyclic-C_{2-6} alkenyl groups;

X is CH;

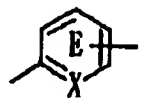
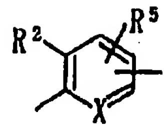
A or A^1 is a C_{1-4} divalent aliphatic hydrocarbon group;

R or R^1 is a C_{1-6} aliphatic hydrocarbon group substituted by (a) oxazolyl or thiazolyl group optionally having 1 or 2 substituents selected from C_{1-6} alkyl groups, C_{2-8} alkenyl groups, C_{3-8} cycloalkyl groups, C_{6-14} aryl groups, C_{7-14} aralkyl groups, C_{6-14} aryl-C_{2-6} alkenyl groups, aromatic heterocyclic groups, aromatic heterocyclic-C_{1-6} alkyl groups, and aromatic heterocyclic-C_{2-6} alkenyl groups, or (b) 4- to 6-membered cyclic amino groups optionally substituted by 1) C_{1-6} alkyl groups, 2) C_{6-14} aryl groups optionally substituted by halogen, C_{1-6} alkoxy groups or trifluoromethyl, 3) 5- or 6-membered heterocyclic groups containing in addition to carbon atoms, as a ring component atom, 1 or 2 nitrogen atoms or 4) 6-membered cyclic amino groups.

Q and Z are oxygen atom;

L and M are hydrogen atom;

ring E, namely the partial formula:

 is  ,

and R^2 and R^5 are independently hydrogen atom or C_{1-4} alkoxy groups.

Preferable examples of the compound represented by the formula (I) or (II) include
5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione;
5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-thiazolylmethyl]-2,4-oxazolidinedione;
5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione;
5-[3-[3,5-dimethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione;
5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(4-methoxyphenyl)piperadin-1-yl]propyl]-2,4-oxazolidinedione;
5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperadin-1-yl)propyl]-2,4-oxazolidinedione; and the like.

As salts of the object compounds (I) and (II) of this invention, pharmaceutically acceptable ones are preferable, as exemplified by salts with an inorganic base, salts with an organic base, salts with an inorganic acid, salts with an organic acid and salts with a basic or acidic amino acid.

Preferable examples of salts with an inorganic base include alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as

calcium salts and magnesium salts; and aluminum salts, ammonium salts or the like. Preferable examples of salts with an organic base include those with, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferable examples of salts with an inorganic acid include those with, for example, hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid or phosphoric acid. Preferable examples of salts with an organic acid include those with, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid or p-toluenesulfonic acid. Preferable examples of salts with a basic amino acid include those with, for example, arginine, lysine or ornithine, and, preferable examples of salts with an acidic amino acid include those with, for example, aspartic acid or glutamic acid. The object compounds (I) and (II) or their salts can be used as hydrate.

The object compounds (I) and (II) or their pharmaceutically acceptable salts of the present invention are low in toxicity and can be used as a medicine as such or as a pharmaceutical composition, for mammals including man (e.g. horse, bovine, dog, cat, rat, mouse, rabbit, swine, monkey), prepared by mixing with a per se known pharmaceutically acceptable carrier, excipient and filler.

The compounds (I) and (II) or their salts of this invention possess an activity of inhibiting the tumor cell growth or an activity of inhibiting tyrosine kinase, thus being useful as anticancer agents. More specifically, these compounds exert excellent effects as antitumor agents on inhibiting principally the

growth of malignant tumors occurring on breast, remote metastatic breast cancer onto organs including e.g. lymph node, bone, brain and liver, and primary and nodal breast cancer aggravated and recurred after treatment, by inhibiting growth of, among human tumor cells, especially human breast cancer cell strains selectively.

And, the compounds (I) and (II) or their salts of this invention are useful also as therapeutic agents of diabetes, based on an action of enhancing insulin-sensitivity.

The compounds (I) and (II) or their salts of this invention are low in toxicity and can be administered safely. For example, oral administration of the compound of Working Example 36 at a dose of 10 mg/kg/day for 14 days to mice killed no test animals, causing no change in body weight.

The administration of a compound (I), (II) or a salt thereof as a medicine to mammals including man is usually performed orally in the form of, for example, tablets, capsules (including soft capsules and microcapsules), powdery preparations and granular preparations, and, depending on cases, non-orally in the form of, for example, injections, suppositories and pellets. The dosage of a compound (I), (II) or a salt thereof varies depending on the administration route, the condition of a patient and the like, in the case of oral administration to a patient (40 to 80 kg body weight) having a malignant tumor, it ranges from 0.05 to 200 mg/kg, preferably from 0.1 to 100 mg/kg, especially from 5 to 50 mg/kg per day, desirably dividing this amount into once to three times a day.

The object compounds (I) and (II) or their salts of this invention, mixed with pharmaceutically acceptable carriers, can be administered orally or non-orally in the form of solid preparations such as

tablets, capsules, granules and powdery preparations; or in the form of liquid preparations such as syrups and injections.

As the pharmaceutically acceptable carriers, use is made of conventional organic or inorganic carriers for pharmaceutical preparations, more specifically, for example, excipients, lubricants, binders and disintegrators for solid preparations; and solvents, solubilizers, suspending agents, isotonizers, buffering agents and local anesthetic agents for liquid preparations. And, upon necessity, such additives as antiseptics, antioxidants, colorants and sweetners are further used.

Preferable examples of excipients include lactose, sucrose, D-mannitol, starch, crystalline cellulose and light silicon dioxide. Preferable examples of lubricants include magnesium stearate, calcium stearate, talc and colloid silica. Preferable examples of binders include crystalline cellulose, sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and polyvinyl pyrrolidine. Preferable examples of disintegrators include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmellose sodium and carboxymethyl starch sodium. Preferable examples of solvents include distilled water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil. Preferable examples of solubilizers include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-amino methane, cholesterol, triethanolamine, sodium carbonate and sodium citrate. Preferable examples of suspending agents include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride and glycerin monostearate; and

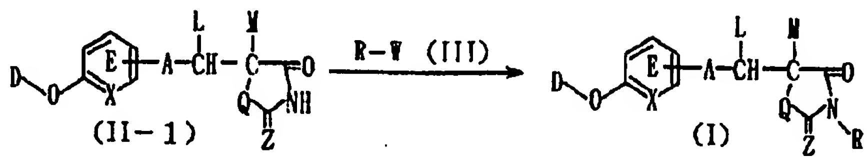
hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose. Preferable examples of isotonizers include sodium chloride, glycerin and D-mannitol. Preferable examples of buffering agents include buffer solutions of phosphates, acetates, carbonates and citrates. Preferable examples of local anesthetic agents include benzyl alcohol. Preferable examples of antiseptics include para-hydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid. Preferable examples of antioxidants include sulfites and ascorbic acid.

The pharmaceutical preparation of this invention can be formulated in accordance with a conventional method, by allowing the object compound (I), (II) or a salt thereof to be contained in an amount of 0.1 to 90% (w/w) relative to the total weight of the preparation.

The compound (II) or a salt thereof of this invention (hereinafter containing the compound (I) or a salt thereof) can be produced by, for example, the following methods. Additionally stating, in the following production methods, excepting the compound of the formula (VI), not only the compounds shown by the respective formulae but also their salts may optionally be used. Examples of these salts include those set forth as the salts of the compounds (I) and (II). And, in each production method, when the product is obtained as a free form, it can be converted to the corresponding salt, and, when the product is obtained as a salt, it can be converted to the free compound in accordance with a conventional method. In the following descriptions, when, for example, NH_2, OH or COOH is included in the substituents, the compounds in which these groups are protected may optionally be

employed as starting compounds, and, after completion of the reaction, the protecting group is removed to produce the object compound.

Method A



wherein each symbol is of the same meaning as defined above.

As the leaving group shown by W, mention is made of, for example, halogen atoms (e.g. chlorine, bromine, fluorine), methanesulfonyloxy, benzonesulfonyloxy and p-toluenesulfonyloxy.

In this method, the compound (I) is produced by subjecting the compound (II-1) to condensation with the compound (III). This reaction is conducted, in accordance with a conventional method, in an adequate solvent in the presence of a base.

As the solvent, mention is made of aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; ketones such as acetone and 2-butanone; N,N-dimethylformamide; dimethyl sulfoxide; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; and a mixed solvent of them.

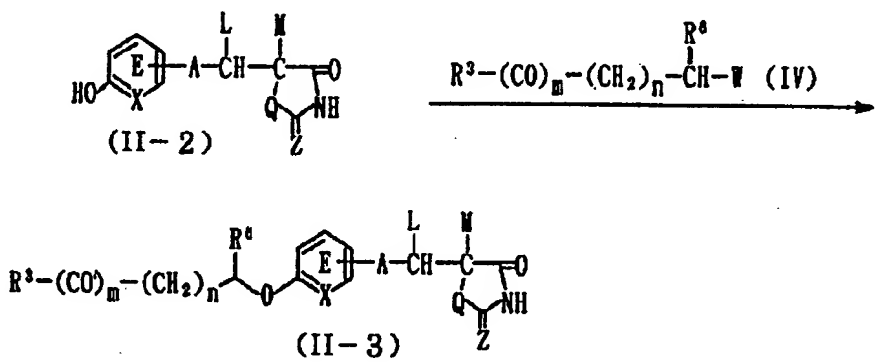
As the base, use is made of, for example, alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; amines such as pyridine, triethylamine and N,N-dimethyl aniline; metal hydrides such as sodium hydride and potassium hydride; and sodium ethoxide, sodium methoxide and potassium tert.-butoxide. The amount of these bases to be employed

ranges, preferably, from 1 to 5 molar equivalents relative to the compound (II-1).

The reaction temperature ranges usually from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 50 hours.

The compound (I) thus obtained can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method B



wherein R^6 stands for hydrogen atom or a lower alkyl group, and other symbols are of the same meaning as defined above.

As the alkyl group shown by R^6, mention is made of C_{1-4} one such as methyl, ethyl, propyl, isopropyl, butyl and tert.-butyl.

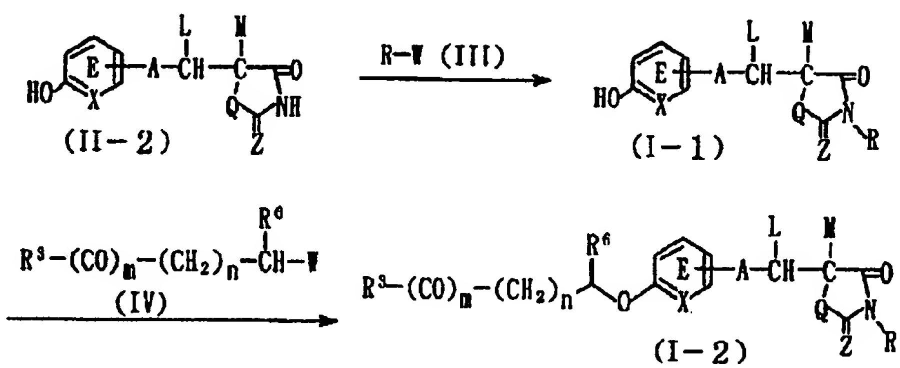
In this method, the compound (II-2) is condensed with the compound (IV) to produce the compound (II-3). This reaction is conduced in a solvent similar to that in Method A and in the presence of a base similar to that in Method A. The amount of the base to be used ranges, preferably, from 2 to 5 molar equivalents relative to the compound (II-2). The amount of the compound (IV) to be used ranges, preferably, from 0.8 to 1.2 molar equivalents relative to the compound (II-

2).

The reaction temperature ranges usually from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 50 hours.

The compound (II-3) thus obtained can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method C



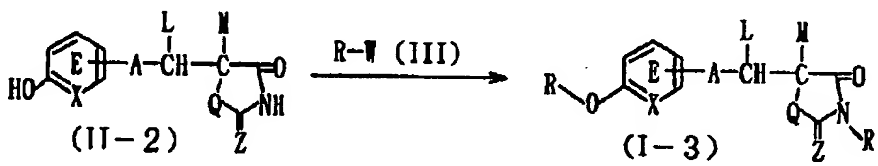
wherein each symbol is of the same meaning as defined above.

In this method, the compound (II-2) is condensed with the compound (III) to produce the compound (I-1), then the compound (I-1) is condensed with the compound (IV) to produce the compound (I-2). The reaction between the compound (II-2) and the compound (III) is conducted in a manner similar to that of Method B. Then, the reaction between the compound (I-1) and the compound (IV) is conducted in a manner similar to that of Method A.

The compounds (I-1) and (I-2) thus obtained can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and

chromatography.

Method D



wherein each symbol is of the same meaning as defined above.

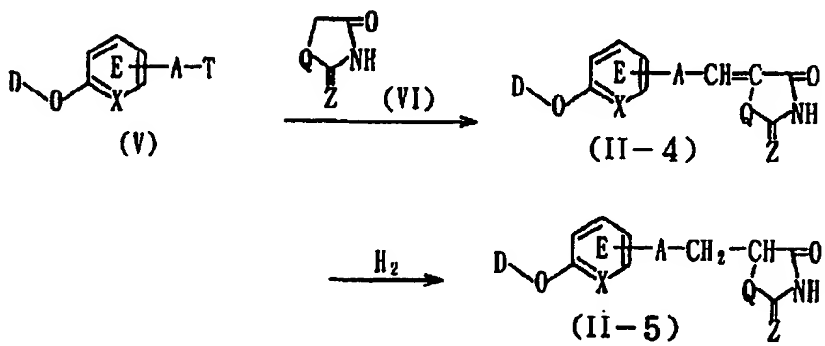
In this method, the compound (II-2) is condensed with the compound (III) to produce the compound (I-3). This reaction is conducted in a solvent similar to that in Method A and in the presence of a base similar to that in Method A. The amount of the base to be used ranges preferably form 2 to 5 molar equivalents relative to the compound (II-2). The amount of the compound (III) to be used ranges preferably from 2 to 5 molar equivalents relative to the compound (II-2).

The reaction temperature ranges usually from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 50 hours.

The compound (I-3) thus obtained can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

The compound (II-1) to be employed in Method A can be produced, in accordance with Method E, from the compound (V).

Method E



wherein T stands for CHO or $-CH(J)_2$ (J stands for a lower alkoxy, a lower alkylthio or a lower acylthio), and other symbols are of the same meaning as defined above.

Examples of the lower alkoxy include C_{1-4} ones such as methoxy, ethoxy, propoxy, isopropoxy and butoxy. Examples of the lower alkylthio include C_{1-4} ones such as methylthio, ethylthio, propylthio, isopropylthio and butylthio. Examples of the lower acyloxy include C_{1-4} ones such as acetyloxy and propionyloxy. In the group $-CH(J)_2$, two J's may optionally be combined with each other to form ethylenedioxy, propylenedioxy and dithiotrimethylene, for example. In other words, $-CH(J)_2$ means a protected aldehyde group.

In this method, the compound (V) is condensed with the compound (VI) to produce the compound (II-4). This condensation reaction is conducted in a solvent in the presence of a base.

Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; N,N-dimethylformamide; dimethyl sulfoxide and acetic acid.

As the base, use is made of sodium alkoxide (e.g. sodium methoxide, sodium ethoxide), potassium carbonate, sodium carbonate, sodium hydride, sodium

acetate, or secondary amines such as piperidine, piperazine, pyrrolidine, morpholine, diethylamine and diisopropylamine. The amount of the compound (VI) to be used ranges from 1 to 10 molar equivalents, preferably from 1 to 5 molar equivalents relative to the compound (V). The amount of the base to be employed ranges from 0.01 to 5 molar equivalents, preferably from 0.05 to 2 molar equivalents, relative to the compound (V).

The reaction temperature ranges from about 0 to 150°C, preferably from 20 to 100°C. The reaction time ranges from 0.5 to 30 hours.

The compound (II-4) thus produced is obtained, in some instances, as a mixture of (E) compound and (Z) compound relative to the double bond at the 5-position of the azolidine ring.

Then, the compound (II-4) is subjected to reduction to produce the compound (II-5). This reduction reaction is conducted, in accordance with a conventional method, in a solvent in the presence of a catalyst under hydrogen atmosphere of 1 to 150 atmospheric pressure.

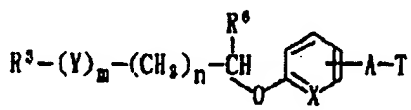
Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; ethyl acetate; acetic acid and a mixture solvent of them. The reaction is conducted more advantageously by employing, as the catalyst, a metal such as a nickel compound and a zinc compound; or a transition metal such as palladium, platinum and rhodium.

The reaction temperature ranges from 0 to 150°C, preferably from 10 to 120°C. The reaction time ranges

from 0.5 to 100 hours.

The compounds (II-4) and (II-5) thus obtained can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

The compound (V) to be employed in Method E can be produced in accordance with, for example the method described in JPA H7(1995)-101945. In the JPA H7(1995)-101945, the method of producing the compound (VII) shown by the following formula is described.

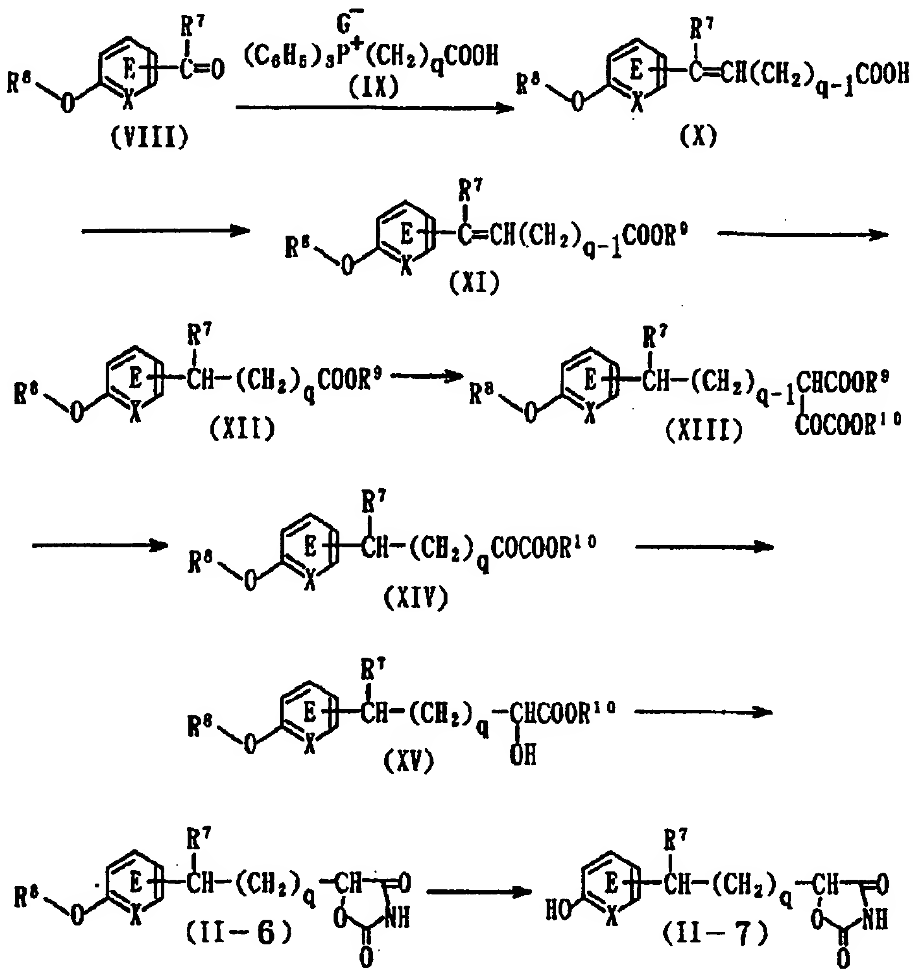


(VII)

wherein each symbol is the same meaning as defined above.

Among the compounds (II-2) to be employed in Method B, Method C and Method D, 2,4-oxazolidinedione derivatives, wherein Q and Z are oxygen atom, and, L and M are hydrogen atom, can be produced in accordance with Method F.

<u>Method F</u>



wherein R^8 stands for isopropyl or benzyl group, R^7 stands for a lower alkyl group, G stands for a halogen atom, q denotes 1,3,4,5 or 6, R^9 and R^{10} independently stand for a lower alkyl group or an aralkyl group, and other symbols are of the same meaning as defined above.

In the above formulae, as the lower alkyl group shown by R^7, mention is made of C_{1-4} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl and isobutyl). As the lower alkyl group shown by R^9, mention is made of C_{1-4} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl). The aralkyl group shown by R^9 means alkyl groups having an aryl

group as the substituent (i.e. an arylalkyl group). As the aryl group, mention is made of, for example, phenyl and naphthyl, and these groups may optionally have, as the substituents, for example, the above-mentioned lower alkyl groups (C_{1-4} ones), halogen atoms (fluorine, chlorine, bromine and iodine), hydroxyl group, and nitro group. As the alkyl group in the arylalkyl group, mention is made of C_{1-4} ones such as methyl, ethyl and propyl. Preferable examples of the aralkyl group include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl, and, among them, benzyl and phenethyl are preferable. As the lower alkyl group or aralkyl group shown by R^{10}, mention is made of similar ones to those shown by R^9. As the halogen atom shown by G, mention is made of chlorine, bromine and iodine.

In this method, firstly, the carboxylic acid derivative (X) is produced by allowing the carbonyl derivative (VIII) to react with the phosphonium salt (IX). The reaction between the compound (VIII) and the compound (IX) is conducted in dimethyl sulfoxide in the presence of sodium hydride. The amount of sodium hydride to be employed ranges from about 2 to 5 molar equivalents relative to the compound (VIII). The amount of the compound (IX) to be used preferably ranges from about 1 to 3 molar equivalents relative to the compound (VIII).

The reaction temperature ranges usually from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 50 hours.

Then, the carboxylic acid derivative (X) is subjected to esterification to produce the compound (XI). This esterification reaction can be conducted by a per se known method. Examples of such method include a method in which the compound (X) is esterified directly with alcohol (R^9OH) in the presence of an

acid; a method in which a reactive derivative of the compound (X) such as acid anhydride, acid halide (acid chloride, acid bromide), imidazolide and a mixed acid anhydride (e.g. anhydride with methyl carbonate, anhydride with ethyl carbonate or anhydride with isobutyl carbonate) to react with alcohol (R^9OH); and a method in which the compound (X) is reacted with R^9-G in the presence of a base.

Then, the compound (XI) is subjected to catalytic reduction to produce the compound (XII). This catalytic reduction can be conducted in substantially the same manner as in the reduction of the compound (II-4) in Method E.

Then, the compound (XII) is allowed to react with oxalic acid ester $(COOR^{10})_2$ in the presence of a base. The reaction of the compound (XII) with oxalic acid ester $(COOR^{10})_2$ is conducted, by a conventional method in a suitable solvent in the presence of a base.

Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxy ethanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; and halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane.

As the base, mention is made of sodium ethoxide, sodium methoxide and potassium tert.-butoxide. The amount of these bases to be employed preferably ranges from about 1 to 5 molar equivalents relative to the compound (XII), and the amount of the oxalic acid ester $(COOR^{10})_2$ to be employed ranges preferably from about 1 to 5 molar equivalents relative to the compound (XII).

The reaction temperature ranges usually from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 50 hours.

The condensed product (XIII) thus obtained is

subjected to decarboxylation reaction to produce α-keto ester (XIV). This decarboxylation reaction is conducted under heating in hydrous dimethyl sulfoxide in the presence of sodium chloride or lithium chloride. The amount of sodium chloride or lithium chloride to be used ranges from 1 to 5 molar equivalents.

The reaction temperature ranges from 50°C to 150°C, preferably from about 80°C to 120°C. The reaction time ranges from 0.5 to 50 hours.

Then, the α-keto ester (XIV) is subjected to reduction to produce the compound (XV). This reduction reaction can be conducted by a per se known method, for example, reduction with a metal hydride, reduction with a metal hydride complex, reduction with diborane and a substituted borane, or catalytic hydrogenation. In other words, this reaction can be conducted by treating the compound (XIV) with a reducing agent. Examples of the reducing agent include alkali metal borohydride (e.g. sodium borohydride and lithium borohydride); metal hydride complex such as lithium aluminum hydride; metal hydride such as sodium hydride; an organotin compound (e.g. triphenyltin hydride), metals and metal salts such as a nickel compound and a zinc compound; a catalytic reduction agent using a transition metal catalyst such as palladium, platinum, rhodium and the like together with hydrogen; and diborane. Above all, use of alkali metal borohydride (e.g. sodium borohydride, lithium borohydride) serves to conduct the the reaction advantageously. This reaction is conducted in an organic solvent which does not interfere with the reaction.

Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; ethers such as diethyl

ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxy ethanol; amides such as N,N-dimethylformamide; and a mixture of them, and, from among these solvents, a suitable one is selectively employed depending on kinds of the reducing agent.

The reaction temperature ranges from -20°C to 150°C, especially preferably from 0°C to 100°C. The reaction time ranges from about 1 to 24 hours.

Then, the compound (XV) is subjected to cyclization reaction to produce 2,4-oxazolidinedione derivative (II-6). The cyclization reaction is conducted by a per se known method such as a method in which the compound (XV) is reacted with alkali metal cyanate; and a method in which the compound (XV) is reacted with urea in the presence of a base.

The reaction between the compound (XV) and alkali metal cyanate (potassium cyanate or sodium cyanate) for example is conducted in a suitable solvent.

Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol, 2-methoxy ethanol and butanol; N,N-dimethylformamide (DMF); dimethyl sulfoxide; acetonitrile; and a mixture of them. The amount of alkali metal cyanate ranges, relative to the compound (XV), from 1 to 10 molar equivalents, preferably from 1 to 5 molar equivalents.

The reaction temperature ranges from 0 to 180°C, preferably from 30 to 150°C. The reaction time ranges from 0.5 to 100 hours.

The alkali metal salt of the compound (II-6) thus obtained is processed with an acid by a conventional method to produce the compound (II-6) as a free form. This process with an acid is conducted in the presence or absence of a suitable solvent.

Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol, 2-methoxy

ethanol and butanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; ethyl acetate; acetonitrile; and a mixture of them.

As the acid, excess amount of an inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid is preferably employed, while an organic acid such as acetic acid, citric acid and tartaric acid may also employed.

Then, by removing R^8 of the compound (II-6), the compound (II-7) is produced.

When R^8 is a benzyl group, the compound (II-6) is subjected to substantially the same catalytic reduction of the compound (II-4) in Method E to produce the compound (II-7).

When R^8 is an isopropyl group, the compound (II-6) is subjected to the reaction with titanium tetrachloride to produce the compound (II-7). The reaction of the compound (II-6) with titanium tetrachloride is conducted in an suitable organic solvent.

As the solvent, use is made of, suitably selectively, for example, aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; ethers such as diethyl ether, tetrahydrofuran and dioxane; or a mixture of them. The amount of titanium tetrachloride to be used ranges from 1 to 10 molar equivalents, preferably from 1 to 5 molar equivalents, relative to the compound (II-6).

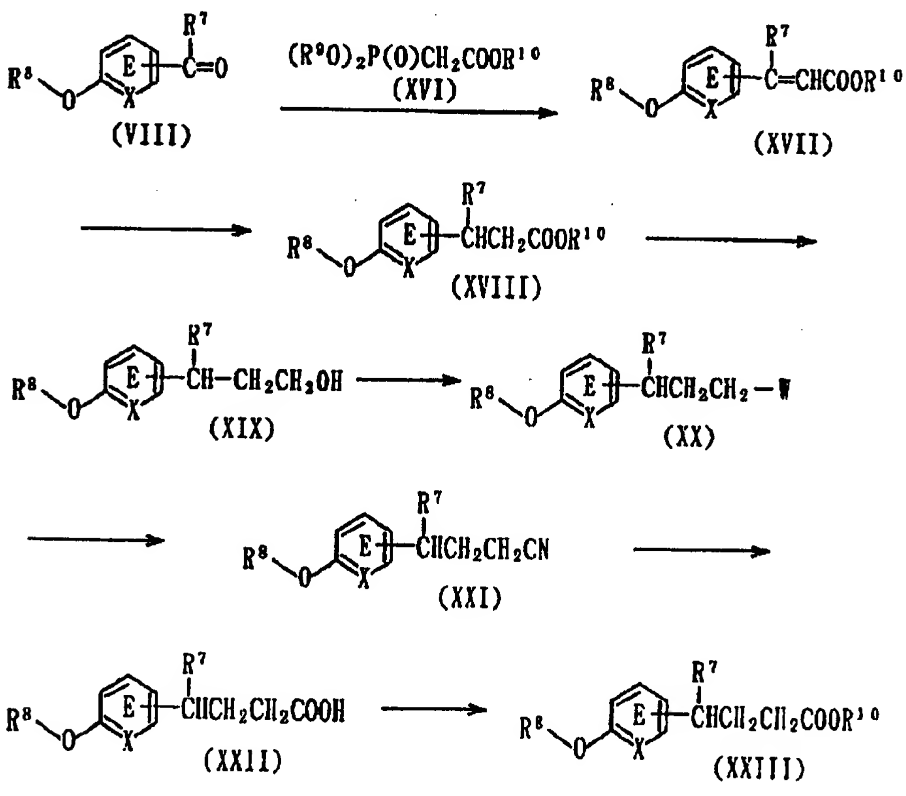
The reaction temperature ranges from -50°C to 100°C, and especially preferably from -20°C to 80°C. The reaction time ranges from about 1 to 24 hours.

The 2,4-oxazolidinedione derivatives (II-6) and (II-7) thus obtained can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

The starting compound (IX) in Method F is produced by the method described in Journal of Medicinal Chemistry, 28, p.287, (1985).

Among the 2,4-oxazolidinedione derivatives represented by the formulae (II-6) and (II-7) set forth in Method F, compounds wherein q is 2 can be derived from the ester derivative (XXIII) produced in accordance with Method G.

Method G



wherein each symbol is of the same meaning as defined above.

In this method, firstly, the carbonyl derivative (VII) is allowed to react with the phosphonoacetic acid derivative (XVI) to produce the unsaturated ester derivative (XVII). The reaction of the compound (VIII) with the compound (XVI) is conducted, in accordance with a conventional method, in an adequate solvent in the presence of a base.

Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol and propanol; N,N-dimethylformamide; dimethyl sulfoxide; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; and a suitable mixture of them.

Examples of the base include alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; amines such as pyridine, triethylamine and N,N-dimethyl aniline; metal hydrides such as sodium hydride and potassium hydride; sodium ethoxide, sodium methoxide and potassium tert.-butoxide. The amount of these bases to be employed ranges, preferably, from about 1 to 5 molar equivalents relative to the compound (VIII). The amount of the compound (XVI) to be employed ranges from 1 to 5 molar equivalents, preferably from about 1 to 3 molar equivalents, relative to the compound (VIII).

The reaction temperature ranges usually from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 30 hours.

Then, the compound (XVII) is subjected to substantially the same catalytic reduction of the compound (II-4) in Method E to produce the compound (XVIII). Further, the compound (XVIII) is subjected to substantially the same reduction of the compound (XIV)

in Method F to produce the alcohol derivative (XIX). The alcohol derivative (XIX) can be led, by a per se known method, for example, chlorination by using thionyl chloride, bromination by using phosphorus tribromide or mesylation by using methanesulfonyl chloride, to the compounds represented by the formula (XX) wherein W is Cl, Br or OSO_2CH_3, respectively.

The compound (XX) is allowed to react with potassium cyanide or sodium cyanide in a suitable solvent to produce the compound (XXI).

Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol, and propanol; N,N-dimethylformamide; dimethyl sulfoxide; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; ketones such as acetone and 2-butanone; and a mixture of them. The amount of potassium cyanide or sodium cyanide to be used ranges preferably from about 1 to 5 molar equivalents relative to the compound (XX).

The reaction temperature ranges usually from 0°C to 150°C, preferably from about 20°C to 100°C. The reaction time ranges from 0.5 to 30 hours.

Then, the compound (XXI) is subjected to hydrolysis to produce the carboxylic acid derivative (XXII). This hydrolysis is conducted, preferably, in an aqueous solvent in the presence of potassium hydroxide or sodium hydroxide. The compound (XXIII) is produced by subjecting the carboxylic acid derivative (XXII) to substantially the same esterification of the compound (X) in Method F.

The ester derivative (XXIII) thus obtained can be isolated and purified by a conventional isolating and purifying means such as concentration, concentration

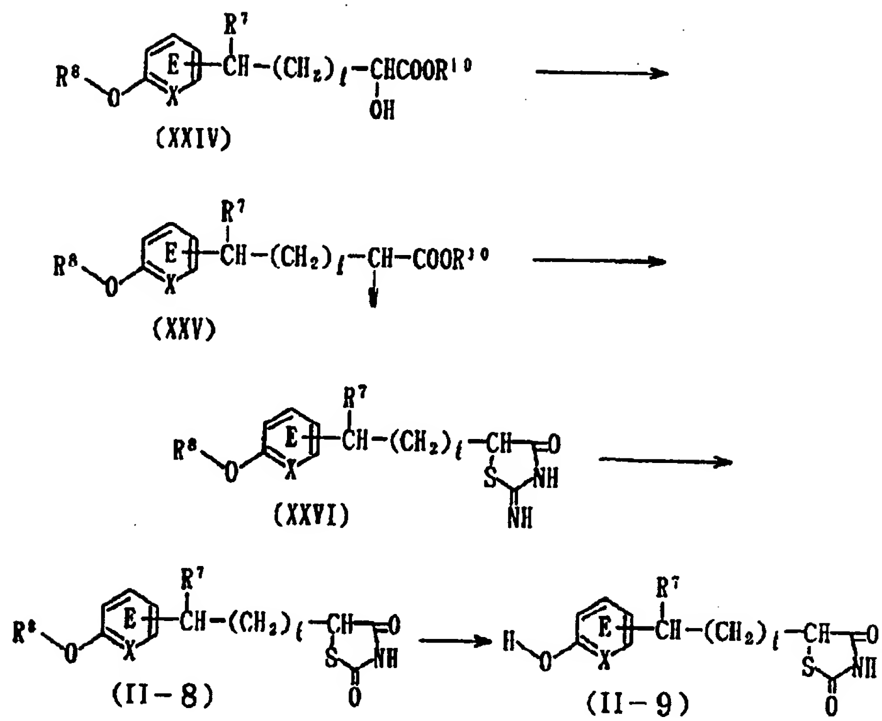
under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

And 2,4-oxazolidinedione derivatives (II-6) and (II-7) wherein q is 2 can be produced by substantially the same procedure as in the production of 2,4-oxazolidinedione derivatives (II-6) and (II-7) from the compound (XII) in Method F.

Among the compounds (II-1) and (II-2) to be employed in Method A, Method B, Method C and Method D, the 2,4-oxazolidinedione derivative wherein A is a bond, and, Q and Z are oxygen atoms can be produced in accordance with the methods described in, for example, JPA H3(1991)-170478, Journal of Medicinal Chemistry, 34, p.1538 (1991), Japanese Patent Application under PCT laid-open under Kohyo No.H5(1994)-506456, WO92/02520 and the like, or the methods analogus thereto.

Among the compounds (II-1) and (II-2) to be employed in Method A, Method B, Method C and Method D, the 2,4-thiazolidinedione derivative, wherein Q is sulfur atom, Z is oxygen atom and, L and M are hydrogen atoms, can be produced by, for example, Method H.

Method H



wherein l denotes an integer of 1 to 6, and other symbols are of the same meaning as defined above.

In this method, starting from the hydroxyester derivative represented by the formula (XXIV) produced by subjecting the compound (XV) produced by Method F and the compound (XXIII) produced by Method G to condensation with oxalic acid ester, decarboxylation and reduction, in substantially the same manner as in Method F,the 2,4-thiazolidinedione derivatives (II-8) and (II-9) are produced.

The reaction from the compound (XXIV) to the compound (XXV) is conducted in substantially the same manner as in the reaction from the compound (XIX) to the compound (XX) in Method G. Then, the compound (XXV) is subjected to a reaction with thiourea to produce the 2-iminothiazolidin-4-one derivative (XXVI). The reaction of the compound (XXV) with thiourea is conducted in a suitable solvent.

Examples of the solvent include aromatic

hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol, propanol and 2-methoxyethanol; N,N-dimethylformamide; dimethyl sulfoxide; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; sulfolan; and a mixture of them. This reaction may optionally be conducted in the presence of a deoxidizing agent (e.g. sodium acetate, potassium acetate) The amount of thiourea to be employed ranges preferably from 1 to 5 molar equivalents relative to the compound (XXV).

The reaction temperature ranges usually from 0°C to 150°C, preferably from about 50°C to 120°C. The reaction time ranges from 0.5 to 30 hours.

The compound (XXVI) is subjected, after isolation or without isolation, to acid hydrolysis to produce the 2,4-thiazolidinedione derivative (II-8). This hydrolysis is conducted in a suitable aqueous solvent. Examples of the solvent include ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol, propanol and 2-methoxyethanol; N,N-dimethylformamide; dimethyl sulfoxide; sulfolan; ketones such as acetone and 2-butanone; and a mixture of them. While the amount of the acid (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, nitric acid) to be employed is usually a large excess relative to the compound (XXVI), it ranges preferably from about 10 to 50 molar equivalents.

The reaction temperature ranges usually from 0°C to 150°C, preferably from about 50°C to 120°C. The reaction time ranges from 0.5 to 30 hours.

The compound (II-8) thus obtained can be derived to the compound (II-9) in substantially the same manner as in the reaction from the compound (II-6) to the

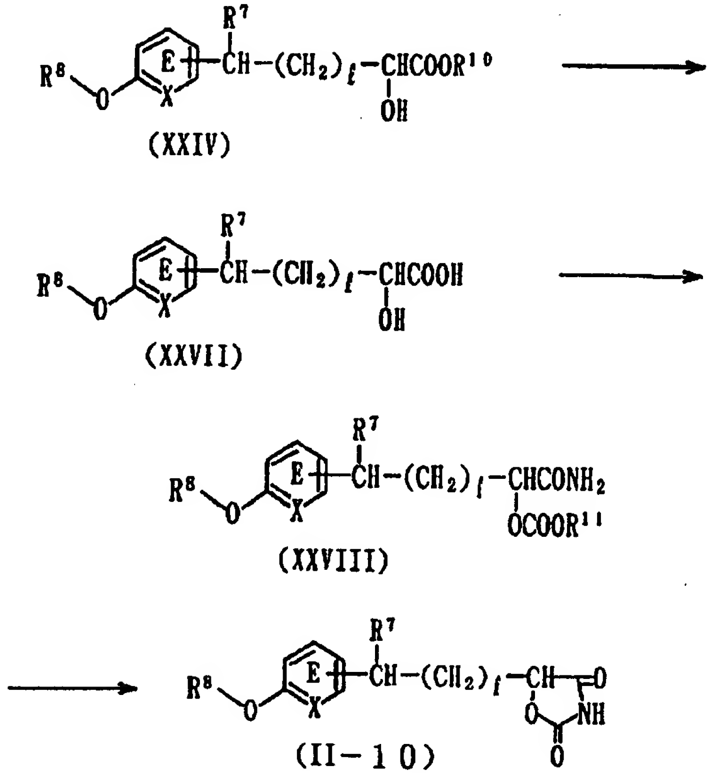
compound (II-7) in Method F.

Among the compounds (II-1) and (II-2) to be employed in Method A, Method B, Method C and Method D, the 2,4-oxazolidinedione derivative wherein A is a bond, Q is sulfur atom and Z is oxygen atom can be produced in accordance with the methods described in, for example, WO94/25026, WO94/05659, JPA under PCT laid-open under Kohyo No.H6(1994)-502146, JPA H1(1989)-131169, JPA S64(1989)-13088, JPA S64(1989)-13076, JPA under PCT laid-open under Kohyo No. H6(1994)-503353, Chemical and Pharmaceutical Bulletin, 30, p.3563 (1982), USP 4,340,605, USP 4,703,052, USP 4,725,610, EP-299,620A, JPA under PCT laid-open under Kohyo No. H5(1993)-506456, JPB H4(1992)-60584, JPB H4(1992)-60583, JPA S61(1986)-271287, JPA H6(1994)-157522, EP-549366-A1, EP-549365A1, JPB H5(1993)-57988, JPA H4(1992)-159282, JPA H4(1992)-225978, JPA H4(1992)-210977, JPB H2(1990)-31079, JPA S64(1989)-38090, JPA S62(1987)-123186, JPA S62(1987)-5981, JPA S62(1987)-5980, WO94/22857, JPA H6(1994)-80677, WO94/01433, JPA H6(1994)-9629, WO93/22445, EP-508740-A1, WO9218501-A1, JPA S63(1988)-139182, JPA S61(1986)-267580, JPA S61(1986)-85372, JPA H5(1993)-194222, JPA H5(1993)-194221, JPB H5(1993)-39928, JPB H5(1993)-39927, JPA H2(1990)-167224, JPA H2(1990)-167225, JPA H2(1990)-167226, JPA S63(1988)-230689, Journal of Medicinal Chemistry, 37, p.3977 (1994), Journal of Medicinal Chemistry, 32, p.421 (1989), Journal of Medicinal Chemistry, 34, p.319 (1991), Journal of Medicinal Chemistry, 34, p.1538 (1991), Arzneimittel-Forschung/Drug Research), 40, p.37 (1990), Journal of Medicinal Chemistry, 35, p.2617 (1992), Chemical and Pharmaceutical Bulletin, 39, p.1440 (1991) and Chemical and Pharmaceutical Bulletin, 30, p.3580 (1982), or the methods analogus thereto.

2,4-Oxazolidinedione derivatives can be produced

in accordance with Method I also.

<u>Method I</u>



wherein R^{11} stands for a lower alkyl group or a substituted phenyl group, and other symbols are of the same meaning as defined above.

As the lower alkyl group shown by R^{11}, mention is made of C_{1-4} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl). As the substituent in the substituted phenyl group shown by R^{11}, mention is made of, for example, the above-mentioned lower alkyl groups (C_{1-4} ones), halogen atoms (fluorine, chlorine, bromine, iodine), hydroxyl group and nitro group.

This method provide a method of producing the 2,4-oxazolidinedione derivative (II-10) starting from α-hydroxyester represented by the formula (XXIV) containing the compound (XV) produced by Method F and the compound which is produced by subjecting the

compound (XXIII) produced by Method G to the method of producing the compound (XV) from the compound (XII) in Method F.

In this method, firstly, the compound (XXIV) is subjected to hydrolysis to produce the α-hydroxycarboxylic acid derivative (XXVII). The hydrolysis is conducted, in accordance with a *per se* known method, in an aqueous solvent in the presence of an acid or a base.

As the solvent, alcohols such as methanol and ethanol are preferable. The amount of the base to be employed ranges from about 1 to 5 molar equivalents, and the amount of the acid to be employed is usually a large excess.

Then, the compound (XXVII) is allowed to react with chlorocarbonic acid ester ($ClCOOR^{11}$), followed by allowing the reaction product to further react with ammonia to produce the compound (XXVIII). The reaction of the compound (XXVII) with chlorocarbonic acid ester ($ClCOOR^{11}$) is conducted, in accordance with a conventional method, in a suitable solvent in the presence of a base.

As the solvent, mention is made of, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; and a mixture of these solvents.

As the base, mention is made of alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; and amines such as pyridine, triethylamine and N,N-dimethyl aniline. The amount of these bases to be employed is preferably about 2 to 5 molar equivalents relative to the compound (XXVII).

The amount of chlorocarbonic acid ester ($ClCOOR^{11}$) to be employed is 2 to 5 molar equivalents, preferably about 2 to 3 molar equivalents, relative to the compound (XXVII).

This reaction temperature ranges usually from -80°C to 50°C, preferably from about -50°C to 30°C. The reaction time ranges from 0.5 to 30 hours.

Subsequently, the product is subjected to reaction with ammonia to produce the compound (XXVIII). This reaction is conducted, usually, by using aqueous ammonia. The reaction temperature ranges from -30°C to 50°C, preferably from about -20°C to 30°C.

The reaction time ranges from 0.5 to 30 hours.

The compound (XXVIII) is led to the 2,4-oxazolidinedione derivative (II-10), in accordance with a conventional method, by processing the compound (XXVIII) with a base in a suitable solvent.

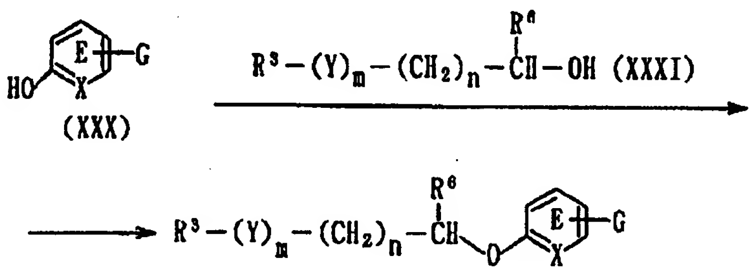
As the solvent, mention is made of, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; acetonitrile; and a mixture solvent of these solvents.

As the base, mention is made of, alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undecen-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); sodium ethoxide, sodium methoxide and potassium tert.-butoxide. The amount of these bases to be employed is preferably about 1 to 5 molar equivalents relative to the compound (XXVIII). The reaction temperature ranges usually from -80°C to 50°C, preferably from about -50°C to 30°C.

The reaction time ranges form 0.5 to 30 hours. The 2,4-oxazolidinedione derivative (II-10) thus obtained can be isolated and purified by a conventional isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

Among the starting compounds (V) in Method E and the starting compounds (VIII) in Method F, the compounds represented by the formula (XXIX) can be produced also by Method J.

Method J



(XXX) (XXXI) (XXIX)

wherein G stands for -A-T, $-C(R^7)=O$; A, T R^7 and other symbols are of the same meaning as defined above.

In this reaction, the compound (XXX) is allowed to react with the compound (XXXI) to produce the compound (XXIX). This reaction is conducted in accordance with a per se known Mitsunobu reaction.

This reaction is conducted in a solvent, preferably, in the presence of triphenylphosphine and diethyl ester of azodicarboxylic acid.

As the solvent, mention is made of, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; and a mixture of them. The respective amounts of triphenylphosphine and diethyl

ester of azodicarboxylic acid to be used are, preferably, about 1 to 5 molar equivalents relative to the compound (XXX), and the amount of the compound (XXXI) to be used is preferably about 1 to 2 molar equivalents relative to the compound (XXX).

The reaction temperature ranges usually from -50°C to 100°C, preferably from about -30°C to 80°C. The reaction time ranges from 0.5 to 50 hours.

The compound (XXIX) thus obtained can be isolated and purified by a conventional isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method K

In this method, when the compounds produced in accordance with Method A, Method B, Method C, Method D, Method E, Method H or Method I contain methoxy group as a substituent on the ring E, these compounds are subjected to demethylation reaction to produce the corresponding phenol derivative.

This reaction is conducted by the reaction with alkyl mercaptan (e.g. ethyl mercaptan, dodecamercaptan) in a solvent in the presence of aluminum chloride.

As the solvent, mention is made of, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; and a mixture of them. The amount of aluminum chloride to be used ranges preferably from about 5 to 20 molar equivalents relative to the methoxy derivative, and the amount of titanium tetrachloride to be used ranges preferably from about 5 to 20 molar equivalents relative to the methoxy derivative.

The reaction temperature ranges usually from -80°C

to 100°C, preferably from about -50°C to 50°C. The reaction time ranges from 0.5 to 50 hours.

The phenol derivatives thus obtained can be isolated and purified by a conventional isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phasic transfer and chromatography.

BEST MODE FOR CARRYING OUT THE INVENTION

The actions of the compounds of this invention are described by means of the following Test Examples.

Test Example 1

Cell growth-inhibiting action in vitro

A 100 μl (2,000 cells) each suspension of human breast cancer cells MDA-MB-453 or human pancreatic carcinoma cells AsPC-1 and, as human normal cells, fibroblast cells MRC5 derived from fetal lung was plated in 96-well microplates and incubated at 37°C in a 5% carbon dioxide incubator. On the following day, a 100 μl each solution of the respective test compounds in serial two-folds dilution was added, followed by incubation for 3 days. The culture medium containing the test compounds was removed, and the cells were washed, to which was added a 0.4% (w/v) solution (dissolved in 1% acetic acid) of the dye SRB (sulforhodamine B) to fix and stain the cell protein. The unbound dye was removed and the plates were washed, to which was then added 200 μl of an extracting solution (10 mM Tris buffer solution) to extract the dye. The absorbance at 540 nm of the absorption wave-length was measured and the cell amount was determined as the amount of protein. The ratio of the remaining amount of protein in each test group, assuming the amount of protein in the control group to which a solution of the test compound was not added as 100%,

was determined to calculate the concentration, IC_{50} value, of the compound required for suppressing the remaining cell amount to 50% of that of the control group.

The results were as shown in [Table 1]. All of the test compounds suppressed the cell-growth of the breast cancer cells MDA-MB-453 at a by far lower concentration than that suppressing the growth of normal cells MRC5. Incidentally, in the following, the test compounds were shown by Working Example Number, for example, the compound of Working Example 36 was shown as "compound 36".

[Table 1]

Cell-growth inhibition test

Compound	IC_{50} (μM)		
	Breast cancer MDA-MB-453	Pancreatic carcinoma AsPC-1	Normal cells MRC5
36	0.038	-	0.37
7	0.006	0.72	>25
8	0.072	0.45	>25

Test Example 2

Breast cancer cell growth-inhibiting action in vitro

A 100 μl (2,000 cells) each suspension of the human cancer cells shown in [Table 2] was plated in 96-well microplates and incubated at 37°C in a 5% carbon dioxide incubator. On the following day, a 100 μl each solution of the respective test compounds in serial two-folds dilution was added, followed by incubation for 3 days. The culture medium containing the test compounds was removed, and the cells were washed, to which was added a 0.4% (w/v) solution (dissolved in 1% acetic acid) of the dye SRB to fix and stain the cell protein. The unbound dye was removed and the plates were washed, to which was then added 200 μl of an

extracting solution (10 mM Tris buffer solution) to extract the dye. The absorbance at 540 nm of the absorption wave-length was measured and the cell amount was determined as the amount of protein. The ratio of the remaining amount of protein in each test group, assuming the amount of protein in the control group to which a solution of the test compound was not added as 100%, was determined to calculate the concentration, IC_{50} value, of the compound required for suppressing the remaining cell amount to 50% of that of the control group.

The results were as shown in [Table 2]. The compounds of Working Example 36 and Working Example 7 of this invention were shown to suppress selectively the growth of human breast cancer strains.

[Table 2]

Cell-growth inhibiting test

Carcinoma	Cell strain	IC_{50} (μM)	
		Compound 36	Compound 7
Breast cancer	MDA-MB-453	0.038	0.006
	MDA-MB-468	0.06	0.004
	T-47D	0.6	0.012
Pancreatic cancer	AsPC-1	–	0.72

Test Example 3

Inhibition of phosphorylation of growth factor receptor tyrosine of human breast cancer

1000 μl (500,000 cells) of a cell suspension of human breast cancer T-47D was plated in 6-well culture plates and incubated at 37°C in a 5% carbon dioxide incubator. On the following day, added was 1000 μl of a solution of the test compound in 10 times stepwise dilution by means of a culture medium containing a 0.1%

bovine fetal albumin in place of blood serum. One hour later, 10 ng/ml of epidermal growth factor (EGF) was added. Five minutes later, the extraction solution was added to suspend the reaction and, at the same time, the protein was extracted. To the extract solution was added antibody against the epidermal growth factor EGF receptor. Then, the epidermal growth factor EGF receptor protein was allowed to precipitate by immunoprecipitation. The precipitate was fractionated by protein electrophoresis, then, the protein in the electrophoresis gel was transferred to a nylon filter. This filter was allowed to react with a phosphorylated tyrosine specific antibody. The reaction product was fluorescent-labeld and allowed to react with a sensitive film. The amount of light in the sensitive film was quantitatively determined by means of an image-analyzing device. Assuming the amount of phosphorylation of EGF-receptor tyrosine of cells in the group to which the epidermal growth factor EGF was added as 100%, the ratios of the amount of phosphorylation in the groups to which solutions of compounds of various concentrations were added were determined.

And, to the human breast cancer cell T-47D, 2 ug/ml of hereglin was added to extract protein in the same manner, to which was added an antibody against human EGF receptor type oncogene HER2 to allow the human EGF receptor type oncogene HER2 protein to precipitate by immunoprecipitation. This precipitate was subjected, in the same manner, to electrophoresis to thereby transfer the protein in the electrophoresis gel into nylon filter. In the same manner, this filter was allowed to react with a phosphorylated tyrosine specific antibody. The reaction product was fluorescent-labeled and allowed to react with a sensitive film. The amount of light in the sensitive

film was quantitatively determined by means of an image analyzing device. Assuming the amount of phosphorylation of HER2 tyrosine of cells in the group to which hereglin was added as 100%, the ratios of the amount of phosphorylation of HER2 tyrosine of cells in the groups, to which solutions of various concentrations were added, were determined.

And, to the human breast cancer cell T-47D, 2 ug/ml of halegrin was added to extract protein in the same manner, to which was added an antibody against human EGF receptor type oncogene HER3 to allow the EGF receptor type oncogene HER3 protein to precipitate by immunoprecipitation. This precipitate was subjected, in the same manner, to electrophoresis to thereby transfer the protein in the electrophoresis gel into nylon filter. In the same manner, this filter was allowed to react with a phosphorylated tyrosine specific antibody. The reaction product was fluorescent-labeled and allowed to react with a sensitive film. The amount of light in the sensitive film was quantitatively determined by means of an image analyzing device. Assuming the amount of phosphorylation of HER3 tyrosine of cells in the group to which hereglin was added as 100%, the ratios of the amount of phosphorylation of HER3 tyrosine of cells in the groups, to which solutions of various concentrations were added, were determined.

The results were as shown in [Table 3]. The compound of Working Example 36 of this invention was shown to inhibit concentration-dependently phosphorylation reaction of the tyrosine residue of the receptor protein, the phosphorylation reaction being caused by activation of the receptor tyrosine kinase due to stimulation of growth factor, when human breast cancer cells were subjected to stimulation with the growth factor EGF and hereglin.

[Table 3]

Inhibition of phosphorylation of receptor tyrosine residue

Growth factor	Receptor	Phosphorylation of tyrosine residue (%)					
		Conc.of cpd. 36	0	0.1	1	10	100 (μM)
EGF	EGF receptor		100	81	59	47	39
Hereglin	HER2		100	100	67	54	16
Hereglin	HER3		100	110	91	19	5

From [Table 1], [Table 2] and [Table 3], the compounds of this invention are found to exhibit an action of inhibiting the activation of receptor tyrosine kinase due to the stimulation of growth factor, and to inhibit the growth of tumor cells, especially to inhibit the growth of breast cancer cells selectively, while showing no cytotoxicity to the growth of normal cells.

The present invention will be illustrated in further detail in the following Reference Examples, Working Examples and Formulation Examples, which are not intended to limit this invention within the scope of these Examples.

Elution in the column chromatography conducted in Reference Examples and Working Examples was carried out while monitoring with TLC (Thin Layer Chromatography). In the TLC monitoring, as the TLC plate, use was made of kieselguhr $60F_{254}$ (70 to 230 mesh) manufactured by Merck & Co., Inc., as the developing solvent, use was made of the same solvent as employed for eluting in the column chromatography, and the detection was conducted with a UV detector. The silica gel for the column was Kieselguhr 60 (70 to 230 mesh) manufactured by Merck & Co. Inc.. NMR spectra show proton NMR and were measured using tetramethylsilane as an internal or external standard with VARIAN Gemini 200 (200 MH_Z type spectrometer). All δ values were expressed in ppm.

And, the abbreviations used in Working Examples have the following meanings.

s:singlet, br:broad, d:doublet, t:triplet, q:guartet, dd:double doublet, td:triple doublet, ddd:doublet doublet doublet, m:multiplet, J:coupling constant, Hz:Hertz.

Reference Example 1

A mixture of cinnamamide (25.3 g) and 1,3-dichloroacetone (20.9 g) was heated at 130 °C for one hour. To the reaction mixture was poured water, which was neutralized with potassium carbonate, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and concentrated. The concentrate was purified by means of a silica gel column chromatography. From the fraction eluted with ether-hexane (1:5, v/v), 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (16.9 g, 47%) was obtained.

Recrystallization from ether-hexane gave colorless needles, m.p. 72-73°C.

Reference Example 2

A mixture of thiocinnamamide (11.7 g), 1,3-dichloroacetone (9.1 g) and ethanol (145 ml) was stirred for one hour under reflux. The reaction mixture was poured into ice-water, which was neutralized with potassium carbonate, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The concentrate was purified by means of a silica gel column chromatography. From the fraction eluted with ether-hexane (1:6, v/v), 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole (9.4 g, 56%) was obtained. Recrystallization from ether-hexane gave colorless plates, m.p. 88-89°C.

Reference Example 3

In substantially the same manner as in Reference Example 1, (E)-3-(2-furyl) acrylic acid amide was allowed to react with 1,3-dichloroacetone to give 4-chloromethyl-2-[(E)-2-(2-furyl)ethenyl]oxazole. Recrystallization from hexane gave pale yellow plates, m.p. 84-85°C

Reference Example 4

In substantially the same manner as in Reference Example 1, (E,E)-5-phenyl-2,4-pentadienamide was allowed to react with 1,3-dichloroacetone to give 4-chloromethyl-2-[(E,E)-4-phenyl-1,3-butadienyl]oxazole. Recrystallization from hexane gave pale yellow needles, m.p. 95-96°C.

Reference Example 5

A mixture of vanillin (50.0 g), isopropyl iodide (82.3 g), potassium carbonate (68.1 g) and N,N-dimethylformamide (DMF) (400 ml) was stirred for 15 hours at 80°C. The mixture was then poured into ice-water, which was subjected to extraction with ethyl

acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The concentrate was subjected to distillation under reduced pressure to give 4-isopropoxy-3-methoxybenzaldehyde (61.2 g, 96%), m.p. 122-124°C/0.25 mmHg.

Reference Example 6

Sodium hydride (60% oil, 12.9 g) was added, in limited amounts at 0°C, to a solution of triethyl phosphonoacetate (72.1 g) and 4-isopropoxy-3-methoxybenzaldehyde (61.2 g) in N,N-dimethylformamide (DMF) (700 ml). The mixture was stirred for one hour at room temperature. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give ethyl 4-isopropoxy-3-methoxycinnamate (75.9 g, 91%). Recrystallization from ethyl acetate-hexane gave colorless needles, m.p. 103-104°C.

Reference Example 7

A solution of aluminum chloride ($AlCl_3$) (6.1 g) in ether (70 ml) was added dropwise, at 0°C, to a suspension of lithium aluminum hydride ($LiAlH_4$) (6.4 g) in ether (270 ml). The mixture was stirred for 10 minutes at room temperature, to which was then added dropwise, at room temperature, a solution of ethyl 4-isopropoxy-3-methoxycinnamate (35.4 g) in ether-tetrahydrofuran (THF) (3:1, 220 ml). The mixture was stirred for 2 hours at room temperature, to which were added dropwise, under ice-cooling, water (170 ml) and 6N H_2SO_4 (230 ml). The organic layer was separated, and the aqueous layer was subjected to extraction with ether. The organic layers were combined, washed with water, dried ($MgSO_4$) and concentrated. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane

(1:2, v/v), was obtained (E)-3-(4-isopropoxy-3-methoxyphenyl)-2-propen-1-ol (27.0 g, 91%).
NMR(δ ppm in $CDCl_3$): 1.37(6H,d,J=6Hz), 1.52(1H,s), 3.87(3H,s), 4.30(2H,dd,J=6&1Hz), 4.52(1H,m), 6.24(1H,dt,J=16&6Hz), 6.55(1H,d,J=16Hz), 6.83(1H,d,J=8Hz), 6.90(1H,dd,J=8&2Hz), 6.94(1H,d,J=2Hz).

Reference Example 8

Activated manganese dioxide (84.5 g) was added to a solution of (E)-3-(4-isopropoxy-3-methoxyphenyl)-2-propen-1-ol (27.0 g) in chloroform (750 ml). The mixture was stirred for 15 hours at room temperature, which was subjected to filtration through a celite layer. The filtrate was concentrated to give 4-isopropoxy-3-methoxycinnamaldehyde (24.2 g, 90%). Recrystallization from ethyl acetate - hexane gave colorless plates, m.p. 93-94°C.

Reference Example 9

Sodium hydride (60% oil, 4.8 g) was added, in limited amounts at 0°C, to a solution of triethyl 4-phosphonocrotonate (30.3 g) and 4-benzyloxybenzaldehyde (23.4 g) in N,N-dimethylformamide (DMF) (110 ml). The mixture was stirred for 15 hours at room temperature. The reaction mixture was poured into 1N HCl (600 ml), which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give ethyl (E,E)-5-(4-benzyloxyphenyl)-2,4-pentadienoate (23.8 g, 70%). Recrystallization from ethyl acetate-hexane gave pale yellow prisms, m.p. 109-110°C.

Reference Example 10

A mixture of ethyl (E,E)-5-(4-benzyloxyphenyl)-2,4-pentadienoate (23.2 g), palladium-carbon (5%, 10.0 g) and tetrahydrofuran (THF) (250 ml) was subjected to catalytic reduction under atmospheric pressure at room temperature. The catalyst was filtered off, and the

filtrate was concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:3, v/v), ethyl 5-(4-hydroxyphenyl)pentanoate (12.5 g, 75%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7Hz), 1.60-1.68(4H,m), 2.32(2H,t,J=7Hz), 2.55(2H,t,J=7Hz), 4.13(2H,q,J=7Hz), 4.97(1H,s), 6.75(2H,d,J=8Hz), 7.03(2H,d,J=9Hz).

Reference Example 11

A mixture of ethyl 5-(4-hydroxyphenyl)pentanoate (12.5 g), benzyl bromide (10.6 g), potassium carbonate (11.7 g) and N,N-dimethylformamide (DMF) (70 ml) was stirred for 3 hours at 100°C. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and then concentrated. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:9, v/v), ethyl 5-(4-benzyloxyphenyl)pentanoate (14.1 g, 80%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7Hz), 1.57-1.67(4H,m), 2.31(2H,t,J=7Hz), 2.57(2H,t,J=7Hz), 4.12(2H,q,J=7Hz), 5.04(2H,s), 6.90(2H,d,J=9Hz), 7.09(2H,d,J=9Hz), 7.31-7.46(5H,m).

Reference Example 12

A solution of ethyl 5-(4-benzyloxyphenyl)pentanoate (14.1 g) and diethyl oxalate (13.2 g) in ethanol (10 ml) was added to an ethanol solution of sodium ethoxide [prepared from sodium (1.35 g) and ethanol (40 ml)]. The mixture was heated for 30 minutes under reflux. The reaction mixture was heated for 30 minutes at 70°C, while distilling off ethanol under reduced pressure. The residue was partitioned between 2N HCl (150 ml) and ethyl acetate (300 ml).

The ethyl acetate layer was washed with water, dried ($MgSO_4$) and then concentrated. The concentrate was dissolved in dimethyl sulfoxide (DMSO) (60 ml) - water (6 m). To the solution was added sodium chloride (2.6 g), and the mixture was stirred for 3 hours at 125°C. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and then concentrated. The concentrate was dissolved in ethanol (100 ml), to which was added dropwise, at 0°C, a solution of sodium borohydride ($NaBH_4$) (0.52 g) in ethanol (20 ml). The mixture was stirred for 30 minutes at 0°C, to which was added acetic acid (1.6 ml). The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, a saturated aqueous solution of sodium hydrogencarbonate and water, successively, which was dried ($MgSO_4$) and then concentrated. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:5, v/v), ethyl 6-(4-benzyloxyphenyl)-2-hydroxyhexanoate (9.5 g, 62%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.28(3H,t,J=7Hz), 1.40-1.83(6H,m), 2.56(2H,t,J=8Hz), 2.74(1H,d,J=6Hz), 4.12-4.28(1H,m), 4.23(2H,q,J=7Hz), 5.04(2H,s), 6.89(2H,d,J=9Hz), 7.09(2H,d,J=9Hz), 7.31-7.46(5H,m).

Reference Example 13

Sodium hydride (60% oil, 14.4 g) was added to dimethyl sulfoxide (300 ml). The mixture was stirred for 30 minutes at 85°C. The mixture was cooled to room temperature, to which was added, in limited amounts at 25-30°C, (5-carboxypentyl)triphenylphosphonium bromide [$(C_6H_5)_3P^-(CH_2)_5COOH.Br^+$] (75.5 g). The mixture was stirred for 15 minutes at room temperature, to which

was then added, in limited amounts under ice-cooling, 4-benzyloxybenzaldehyde (31.8 g). The reaction mixture was stirred for 30 minutes at room temperature, which was poured into ice-water and acidified, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and then concentrated. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:2, v/v), 7-(4-benzyloxyphenyl)-6-heptenoic acid (31.0 g, 67%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 94-95°C

Reference Example 14

To a mixture of 7-(4-benzyloxyphenyl)-6-heptenoic acid (29.0 g) and ethanol (500 ml) was added concentrated sulfuric acid (0.5 ml). The mixture was heated for 8 hours under reflux. The reaction mixture was concentrated under reduced pressure, which was poured into ice-water, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and then concentrated to give ethyl 7-(4-benzyloxyphenyl)-6-heptenoate (31.6 g).
NMR(δ ppm in $CDCl_3$): 1.24(3H,t,J=7Hz), 1.40-1.60(2H,m), 1.60-1.80(2H,m), 2.15-2.45(4H,m), 4.11(2H,q,J=7Hz), 5.05&5.06(2H,each s), 5.54(0.6H,double t,J=11.6&7.2Hz), 6.05(0.4H,double t,J=15.8&7.2Hz), 6.33(0.4H,d,J=15.8Hz), 6.35(0.6H,d,J=11.6Hz), 6.85-7.0(2H,m), 7.15-7.50(5H,m).

Reference Example 15

A mixture of ethyl 7-(4-benzyloxyphenyl)-6-heptenoate (31.5 g), platinum dioxide (PtO_2) (0.8 g) and ethanol (300 ml) was subjected to catalytic reduction at room temperature under hydrogen pressure of 4 kgf/cm^2. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was subjected to a silica gel column

chromatography. From the fraction eluted with ethyl acetate - hexane (1:1, v/v), ethyl 7-(4-benzyloxyphenyl)heptanoate (30.1 g, 95%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7Hz), 1.25-1.40(4H,m), 1.50-1.70(4H,m), 2.28(2H,t,J=7.3Hz), 2.54(2H,t,J=7.3Hz), 4.12(2H,q,J=7.2Hz), 5.04(2H,s), 6.89(2H,d,J=8.6Hz), 7.08(2H,d,J=8.6Hz), 7.3-7.5(5H,m).

Reference Example 16

Ethyl 7-(4-benzyloxyphenyl)heptanoate was subjected to substantially the same reaction as in Reference Example 12 to give ethyl 8-(4-benzyloxyphenyl)-2-hydroxyoctanoate. Recrystallization from ether-hexane gave colorless needles, m.p. 52-53°C

Reference Example 17

Ethyl 3-(4-benzyloxyphenyl)propionate was subjected to substantially the same reaction as in Reference Example 12 to give ethyl 4-(4-benzyloxyphenyl)-2-hydroxybutanoate. Recrystallization from hexane gave colorless crystals, m.p. 51-52°C.

Reference Example 18

To a mixture of ethyl 4-(4-benzyloxyphenyl)-2-hydroxybutanoate (35.2 g) and ethanol (200 ml) was added 1N NaOH (240 ml). The mixture was stirred for one hour (0-25°C), then for 40 minutes at 60-70°C. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The aqueous layer was acidified and subjected to extraction with ethyl acetate. This ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then, concentrated to give 4-(4-benzyloxyphenyl)-2-hydroxybutanoate (28.8 g, 84%). Recrystallization from ethyl acetate - hexane gave colorless crystals, m.p. 157-158°C.

Reference Example 18

Triethylamine (20.7 g) was added dropwise, at -

30°C, to a solution of 4-(4-benzyloxyphenyl)-2-hydroxybutanoic acid (28.0 g) in tetrahydrofuran (THF) (400 ml). To the mixture was, then, added dropwise ethyl chlorocarbonate (22.3 g) at the same temperature. The reaction mixture was stirred for 2.5 hours at temperatures ranging from -25 to -10°C. The reaction mixture was then added dropwise at 0°C to a conc. aqueous ammonia (25%, 100 ml). The mixture was stirred for 40 minutes at 0°C, which was then poured into water. Resulting crystalline precipitate was collected by filtration to give 4-(4-benzyloxyphenyl)-2-ethoxycarbonyloxybutanamide (30.9 g, 88%). Recrystallization from acetone-hexane gave yellow prisms, m.p. 160-161°C.

Reference Example 20

In substantially the same manner as in Reference Example 6, 4-isopropoxybenzaldehyde was allowed to react with triethyl phosphonoacetate to give ethyl 4-isopropoxycinnamate as an oily product.

NMR(δ ppm in $CDCl_3$): 1.33(3H,t,J=7Hz), 1.35(6H,d,J=6Hz), 4.25(2H,q,J=7Hz), 4.5-4.7(1H,m), 6.30(1H,d,J=16Hz), 6.87(2H,d,J=9Hz), 7.46(2H,d,J=9Hz), 7.63(1H,d,J=16Hz).

Reference Example 21

Ethyl 4-isopropoxycinnamate was subjected to reduction with diisobutyl aluminum hydride to give (E)-3-(4-isopropoxyphenyl)-2-propen-1-ol as an oily product.

NMR(δ ppm in $CDCl_3$): 1.33(6H,d,J=6Hz), 1.38(1H,t,J=6Hz), 4.30(2H,dt,J=6&1.5Hz), 4.45-4.65(1H,m), 6.23(1H,dt,J=16&6Hz), 6.56(1H,d,J=16Hz), 6.84(2H,d,J=8.5Hz), 7.31(2H,d,J=8.5Hz).

Reference Example 22

In substantially the same manner as in Reference Example 8, (E)-3-(4-isopropoxyphenyl)-2-propen-1-ol was subjected to oxidation with manganese dioxide to give

4-isopropoxycinnamaldehyde as an oily product.
NMR(δ ppm in $CDCl_3$): 1.37(6H,t,J=6Hz), 4.5-4.7(1H,m), 6.61(1H,dd,J=16&8Hz), 6.92(2H,d,J=9Hz), 7.42(1H,d,J=16Hz), 7.51(2H,d,J=9Hz), 9.65(1H,d,J=8Hz).

Reference Example 23

A hexane solution of n-butyl lithium (1.6M, 15.6 ml) was added dropwise at -15°C to a mixture of (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (10.74 g) and tetrahydrofuran (110 ml). This mixture was stirred for one hour at the same temperature, to which was then added 3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzaldehyde (6.74 g). The mixture was stirred for 4 hours at 50°C. The reaction mixture was poured into ice-water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with 0.1N HCl, water and a saturated aqueous saline solution, successively, followed by drying ($MgSO_4$). The solvent was then distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:2, v/v), 2-[2-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]vinyl]-1,3-dioxolan (4.84 g) was obtained as an oily product. This oily product (4.84 g) was dissolved in tetrahydrofuran (90 ml), to which was added palladium-carbon (5%, 50% wet, 1.8 g). The mixture was subjected to catalytic reduction under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated, which was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:3, v/v), 2-[2-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]ethyl]-1,3-dioxolan (3.03 g, 37%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 90-91°C.

Reference Example 24

A mixture of 2-[2-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]ethyl]-1,3-dioxolan (2.73 g) and aqueous solution of acetic acid (50%, 75 ml) was stirred for 3 hours at 80°C. The reaction mixture was concentrated under reduced pressure. The concentrate was poured into water, which was made basic with potassium carbonate, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and, then, dried ($MgSO_4$). The solvent was distilled off to give 3-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propionaldehyde (2.09 g, 86%). Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 85-86°C.

Reference Example 25

A mixture of 3-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propionaldehyde (1.79 g), sodium cyanide (0.3 g), acetic anhydride (0.62 g), benzyltributylammonium chloride (0.79 g), water (12 ml) and dichloromethane (35 ml) was stirred for 15 hours at room temperature. The organic layer was separated, washed with water and dried ($MgSO_4$). The solvent was distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:3, v/v), 2-acetoxy-4-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]butyronitrile (2.0 g, 94%) was obtained.

NMR(δ ppm in $CDCl_3$): 2.14(3H,s), 2.12-2.31(2H,m), 2.41(3H,s), 2.78(2H,t,J=8Hz), 3.87(3H,s), 5.04(2H,s), 5.27(1H,t,J=7Hz), 6.70(1H,dd,J=8&2Hz), 6.71(1H,d,J=2Hz), 7.00(1H,d,J=9Hz), 7.42-7.47(3H,m), 7.99-8.04(2H,m).

Reference Example 26

A mixture of 2-acetoxy-4-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]butyronitrile (2.0 g), 6N HCl (24 ml) and dioxane (12 ml) was stirred for 4

hours under reflux. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off. To the residual oily substance was added ethanolic hydrochloride (10%, 24 ml). The mixture was stirred for 1.5 hour under reflux. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:2, v/v), ethyl 2-hydroxy-4-(4-hydroxy-3-methoxyphenyl)butanoate (0.73 g, 60%) was obtained.

NMR(δ ppm in $CDCl_3$): 1.29(3H,t,J=7Hz), 1.81-2.17(2H,m), 2.70(2H,t,J=8Hz), 2.84(1H,d,J=5Hz), 3.88(3H,s), 4.13-4.19(1H,m), 4.22(2H,q,J=7Hz), 5.50(1H,s), 6.70(1H,dd,J=7&2Hz), 6.72(1H,s), 6.84(1H,d,J=9Hz).

Reference Example 27

Sodium borohydride (1.41 g) was added, in limited amounts at 0°C, to a solution of 4-acetyl-5-methyl-2-phenyloxazole (15.0 g) in ethanol (100 ml). The mixture was stirred for one hour at the same temperature, and for one hour at room temperature. The reaction mixture was poured into water, which was neutralized with 2N HCl to give 1-(5-methyl-2-phenyl-4-oxazolyl)ethanol (13.0 g, 86%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 101-102°C.

Reference Example 28

To a mixture of 1-(5-methyl-2-phenyl-4-oxazolyl)ethanol (5.0 g), vanillin (3.75 g), triphenyl phosphine (Ph_3P) (7.1 g) and tetrahydrofuran (THF) (80 ml) was added dropwise, under ice-cooling, diethyl

azodicarboxylate (DEAD) (4.71 g). The mixture was stirred for 8 hours at room temperature. Then, the reaction mixture was concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:4, v/v), 3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (4.48 g, 54%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 104-105°C.

Reference Example 29

In substantially the same manner as in Reference Example 6, 3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde was allowed to react with triethyl phosphonoacetate to give ethyl 3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamate. Recrystallization from acetone-isopropyl ether gave colorless needles, m.p. 121-122°C.

Reference Example 30

To a solution of ethyl 3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamate (5.05 g) in dichloromethane (100 ml) was added dropwise at 0 °C a toluene solution (1M, 31.0 ml) of diisobutyl aluminum hydride. The mixture was stirred for one hour at room temperature. To the reaction mixture was added methanol (2.0 ml), which was poured into 2N hydrochloric acid, followed by extraction with chloroform. The chloroform layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off to give (E)-3-[3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2-propen-1-ol (4.50 g, 99%). NMR(δ ppm in $CDCl_3$): 1.44(1H,br t,J=6.5Hz), 1.75(3H,d,J=6.5Hz), 2.28(3H,s), 3.88(3H,s), 4.25-4.35(2H,m), 5.37(1H,q,J=6.5Hz), 6.23(1H,dt,J=16&6Hz), 6.52(1H,dt,J=16&1.5Hz), 6.8-6.95(3H,m), 7.35-7.5(3H,m), 7.95-8.05(2H,m).

Reference Example 31

In substantially the same manner as in Reference Example 8, (E)-3-[3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2-propen-1-ol was subjected to oxidation with activated manganese dioxide to give 3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamaldehyde. Recrystallization from acetone-isopropyl ether gave colorless needles, m.p. 152-153°C.

Reference Example 32

Sodium hydride (60% oil, 8.43 g) was added, in limited amounts at 0°C, to a solution of 4-benzyloxy-3-methoxybenzaldehyde (46.4 g) and triethyl phosphonocrotonate (50.3 g) in N,N-dimethylformamide (DMF) (190 ml). This mixture was stirred for 15 hours at room temperature, which was poured into 1N HCl (1 L), followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:3, v/v), ethyl (E,E)-5-(4-benzyloxy-3-methoxyphenyl)-2,4-pentadienoate (38.3 g, 59%). Recrystallization from ethyl acetate - hexane gave pale yellow needles, m.p. 85-86°C.

Reference Example 33

In substantially the same manner as in Reference Example 10, ethyl (E,E)-5-(4-benzyloxy-3-methoxyphenyl)-2,4-pentadienoate was subjected to catalytic reduction to give ethyl 5-(4-hydroxy-3-methoxyphenyl)pentanoate.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7Hz), 1.61-1.66(4H,m), 2.32(2H,t,J=7Hz), 2.56(2H,t,J=7Hz), 3.88(3H,s), 4.12(2H,q,J=7Hz), 5.46(1H,s), 6.66(1H,dd,J=8&2Hz), 6.83(1H,d,J=9Hz).

Reference Example 34

A mixture of ethyl 5-(4-hydroxy-3-methoxyphenyl)pentanoate (27.92 g), benzyl bromide (20.82 g), potassium carbonate (22.9 g) and N,N-dimethylformamide (DMF) (140 ml) was stirred for 15 hours at 90°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:6, v/v), ethyl 5-(4-benzyloxy-3-methoxyphenyl)pentanoate (31.64 g, 84%) was obtained.
NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7Hz), 1.61-1.66(4H,m), 2.32(2H,t,J=7Hz), 2.56(2H,t,J=7Hz), 3.88(3H,s), 4.12(2H,q,J=7Hz), 5.12(2H,s), 6.64(1H,dd,J=8&2Hz), 6.72(1H,d,J=2Hz), 6.80(1H,d,J=8Hz), 7.28-7.47(5H,m).

Reference Example 35

In substantially the same manner as in Reference Example 12, ethyl 5-(4-benzyloxy-3-methoxyphenyl)pentanoate was condensed with diethyl oxalate, and the condensate was subjected to decarboxylation, followed by subjecting the reaction mixture to reduction with sodium borohydride to give ethyl 6-(4-benzyloxy-3-methoxyphenyl)-2-hydroxyhexanoate.
NMR(δ ppm in $CDCl_3$): 1.27(3H,t,J=7Hz), 1.43-1.79(6H,m), 2.55(2H,t,J=8H), 2.73(1H,d,J=6Hz), 3.88(3H,s), 4.12-4.17(1H,m), 4.23(2H,q,J=7Hz), 5.12(2H,s), 6.63(1H,dd,J=8&2Hz), 6.72(1H,d,J=2Hz), 6.79(1H,d,J=8Hz), 7.26-7.46(5H,m).

Reference Example 36

In substantially the same manner as in Reference Example 6, 4-benzyloxy-3-ethoxybenzaldehyde was allowed to react with triethyl phosphonoacetate to give ethyl 4-benzyloxy-3-ethoxycinnamate. Recrystallization from isopropyl ether - hexane gave colorless needles, m.p.

74.5-75°C.

Reference Example 37

In substantially the same manner as in Reference Example 10, ethyl 4-benzyloxy-3-ethoxycinnamate was subjected to catalytic reduction to give ethyl 3-(3-ethoxy-4-hydroxyphenyl)propionate.

NMR(δ ppm in $CDCl_3$): 1.24(3H,t,J=7Hz), 1.44(3H,t,J=7Hz), 2.57(2H,t,J=7.7Hz), 2.87(2H,t,J=7.7Hz), 4.09(2H,q,J=7Hz), 4.13(2H,q,J=7Hz), 5.54(1H,s), 6.69(1H,d,J=8.4Hz), 6.70(1H,s), 6.84(1H,d,J=8.4Hz).

Reference Example 38

In substantially the same manner as in Reference Example 38, ethyl 3-(3-ethoxy-4-hydroxyphenyl)propionate was allowed to react with benzyl bromide to give ethyl 3-(4-benzyloxy-3-ethoxyphenyl)propionate.

NMR(δ ppm in $CDCl_3$): 1.23(3H,t,J=7Hz), 1.45(3H,t,J=7Hz), 2.58(2H,t,J=7.6Hz), 2.87(2H,t,J=7.6Hz), 4.09(2H,q,J=7Hz), 4.12(2H,q,J=7Hz), 5.11(2H,s), 6.66(1H,dd,J=8.3&1.9Hz), 6.76(1H,d,J=1.9Hz), 6.82(1H,d,J=8.3Hz), 7.23-7.61(5H,m).

Reference Example 39

In substantially the same manner as in Reference Example 12, starting from ethyl 3-(4-benzyloxy-3-ethoxyphenyl)propionate, 4-(4-benzyloxy-3-ethoxyphenyl)-2-hydroxybutanoate was obtained. Recrystallization from ethyl acetate - isopropyl ether gave colorless needles, m.p. 62-63°C.

Reference Example 40

In substantially the same manner as in Reference Example 6, 3-benzyloxy-4-methoxybenzaldehyde was allowed to react with triethyl phosphonoacetate to give ethyl 3-benzyloxy-4-methoxycinnamate. Recrystallization from ether-hexane gave colorless

needles, m.p. 95-96°C.

Reference Example 41

In substantially the same manner as in Reference Example 10, ethyl 3-benzyloxy-4-methoxycinnamate was subjected to catalytic reduction to give ethyl 3-(3-hydroxy-4-methoxyphenyl)propionate.

NMR(δ ppm in $CDCl_3$): 1.24(3H,t,J=7Hz), 2.57(2H,t,J=7.6Hz), 2.86(2H,t,J=7.6Hz), 3.86(3H,s), 4.13(2H,q,J=7.2Hz), 5.58(1H,s), 6.68(1H,dd,J=8.2&2Hz), 6.77(1H,d,J=8.2Hz), 6.78(1H,d,J=2Hz).

Reference Example 42

In substantially the same manner as in Reference Example 34, ethyl 3-(3-hydroxy-4-methoxyphenyl)propionate was allowed to react with benzyl bromide to give ethyl 3-(3-benzyloxy-4-methoxyphenyl)propionate. Recrystallization from hexane gave colorless needles, m.p. 49.5-50.5°C

Reference Example 43

In substantially the same manner as in Reference Example 12, starting from ethyl 3-(3-benzyloxy-4-methoxyphenyl)propionate, ethyl 4-(3-benzyloxy-4-methoxyphenyl)-2-hydroxybutanoate was obtained. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 93-94°C.

Reference Example 44

In substantially the same manner as in Reference Example 34, syringaldehyde was allowed to react with benzyl bromide to give 4-benzyloxy-3,5-dimethoxybenzaldehyde. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 65-66°C.

Reference Example 45

In substantially the same manner as in Reference Example 6, 4-benzyloxy-3,5-dimethoxybenzaldehyde was allowed to react with triethyl phosphonoacetate to give ethyl 4-benzyloxy-3,5-dimethoxycinnamate. Recrystallization form ether-hexane gave colorless

plates, m.p. 68-69°C.

Reference Example 46

In substantially the same manner as in Reference Example 30, ethyl 4-benzyloxy-3,5-dimethoxycinnamate was subjected to catalytic reduction with diisobutyl aluminum hydride to give (E)-3-(4-benzyloxy-3,5-dimethoxyphenyl)-2-propen-1-ol. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 72-73°C.

Reference Example 47

In substantially the same manner as in Reference Example 8, (E)-3-(4-benzyloxy-3,5-dimethoxyphenyl)-2-propen-1-ol was subjected to oxidation with activated manganese dioxide to give 4-benzyloxy-3,5-dimethoxycinnamaldehyde. Recrystallization from ethyl acetate - hexane gave colorless plates, m.p. 114-115°C

Reference Example 48

A mixture of 4-isopropoxybenzaldehyde (37.3 g), sodium pyruvate (25.0 g), sodium hydrogencarbonate (19.1 g), water (150 ml) and methanol (150 ml) was stirred for 4 hours under reflux. To the mixture was added sodium pyruvate (25.0 g), which was stirred for further 20 hours under reflux. The reaction mixture was poured into water, which was washed with ether. The aqueous layer was acidified with 6N HCl, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), and, then, the solvent was distilled off to give an oily substance. The oily substance was dissolved in hydrochloric acid - ethanol (5%, 80 ml), which was stirred for 30 minutes at 80°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), and, then, the solvent was distilled off. The residue was subjected to a silica gel column chromatography. From the

fraction eluted with ethyl acetate - hexane (1:4, v/v), ethyl (E)-(4-isopropoxybenzylidene)pyruvate (21.6 g, 36%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.37(6H,t,J=6Hz), 1.41(3H,t,J=6Hz), 4.39(2H,q,J=7Hz), 4.55-4.75(1H,m), 6.91(2H,d,J=9Hz), 7.23(1H,d,J=16Hz), 7.58(2H,d,J=9Hz), 7.83(1H,d,J=16Hz).

Reference Example 49

In acetic acid - ethanol (20%, 500 ml) was dissolved ethyl (E)-(4-isopropoxybenzylidene)pyruvate (19.0 g). To the solution was added palladium-carbon (5%, 50% wet, 3.0 g). The mixture was subjected to catalytic reduction under one atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:4, v/v), ethyl 2-hydroxy-4-(4-isopropoxyphenyl)butyrate (11.2 g, 58%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.29(3H,t,J=7Hz), 1.32(3H,t,J=6Hz), 1.8-2.2(2H,m), 2.65-2.75(2H,m), 2.80(1H,d,J=5.5Hz), 4.1-4.25(1H,m), 4.21(2H,q,J=7Hz), 4.4-4.6(1H,m), 6.81(2H,d,J=8.5Hz), 7.10(2H,d,J=8.5Hz).

Reference Example 50

To a solution of ethyl 2-hydroxy-4-(4-isopropoxyphenyl)butyrate (5.0 g) in pyridine (50 ml) was added dropwise thionyl chloride (2.68 g) at room temperature. The mixture was stirred for one hour. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then the solvent was distilled off, and the residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:9, v/v), ethyl 2-chloro-4-(4-isopropoxyphenyl)butyrate (1.45 g, 27%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.29(3H,t,J=7Hz), 1.32(6H,t,J=6Hz), 2.1-2.35(2H,m), 2.6-2.9(2H,m), 4.15-4.3(3H,m), 4.4-4.6(1H,m), 6.82(2H,d,J=8.5Hz), 7.09(2H,d,J=8.5Hz).

Reference Example 51

Sodium hydride (60% oil, 1.05 g) was added, under ice-cooling, to a mixture of 2-(1,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide (51.0 g) and N,N-dimethylformamide (DMF) (200 ml). This mixture was stirred for 15 minutes at the same temperature, to which was added 4-isopropoxybenzaldehyde (18.0 g). The mixture was stirred for 5 hours at temperatures ranging from 80 to 85°C. The reaction mixture was poured into water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous saline solution, successively, which was dried ($MgSO_4$), then the solvent was distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:4, v/v), an oily product (14.5 g) was obtained. This oily product was dissolved in ethanol (250 ml), to which was added palladium-carbon (5%, 50% wet, 5.0 g). The mixture was subjected to catalytic reduction at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:5, v/v), 2-[3-(4-isopropoxyphenyl)propyl]-1,3-dioxolan (6.70 g, 24%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.32(6H,d,J=6Hz), 1.6-1.8(4H,m), 2.5-2.65(2H,m), 3.8-4.0(4H,m), 4.8-4.9(1H,m), 6.80(2H,d,J=8.5Hz), 7.07(2H,d,J=8.5Hz).

Reference Example 52

4-Benzyloxybenzaldehyde (2.4 g) was added to a mixture of (7-carboxyheptyl)triphenylphosphonium bromide [$(C_6H_5)_3P^-(CH_2)_7COOH.Br^+$] (6.02 g), sodium hydride (60%, oil, 1.13 g) and dimethyl sulfoxide (100 ml) - tetrahydrofuran (100 ml). The mixture was stirred for 4 hours at 40°C. The reaction mixture was poured into ice-water, which was acidified, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), which was then concentrated. The residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:2), 9-(4-benzyloxyphenyl)-8-nonenoic acid (2.57 g, 67%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 81-82°C.

Reference Example 53

To a mixture of 9-(4-benzyloxyphenyl)-8-nonenoic acid (4.5 g) and ethanol (70 ml) was added conc. sulfuric acid (0.1 ml). The mixture was heated for 8 hours under reflux. The reaction mixture was concentrated under reduced pressure, which was poured into ice-water, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give ethyl 9-(4-benzyloxyphenyl)-8-nonenoate (4.35%, 89%).
NMR(δ ppm in $CDCl_3$): 1.24(3H,t,J=7.2Hz), 1.20-1.70(8H,m), 2.10-2.40(4H,m), 4.12(2H,q,J=7.2Hz), 5.05&5.07(2H,each s), 5.42(0.6H,double t,J=11.6&7.4Hz), 6.06(0.4H,double t,J=15.8&6.8Hz), 6.27-6.36(1H,m), 6.87-7.47(9H,m).

Reference Example 54

A mixture of ethyl 9-(4-benzyloxyphenyl)-8-nonenoate (18.7 g), platinum dioxide (PtO_2) (0.4 g) and ethanol (150 ml) was subjected to catalytic reduction at room temperature under hydrogen pressure of 4 kgf/cm^2. The catalyst was filtered off, and the

filtrate was concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:5), ethyl 9-(4-benzyloxyphenyl)nonanoate (10.57, 56%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7.0Hz), 1.20-1.70(12H,m), 2.28(2H,t,J=7.8Hz), 2.53(2H,t,J=7.4Hz), 4.12(2H,q,J=7.0Hz), 5.03(2H,s), 6.89(2H,d,J=8.4Hz), 7.08(2H,d,J=8.4Hz), 7.20-7.46(5H,m).

Reference Example 55

In substantially the same manner as in Reference Example 12, starting from ethyl 9-(4-benzyloxyphenyl)nonanoate, ethyl 10-(4-benzyloxyphenyl)-2-hydroxydecanoate was obtained. Recrystallization from ethyl acetate - hexane gave colorless crystals, m.p. 40-41°C.

Reference Example 56

A solution of ethyl 7-(4-benzyloxyphenyl)heptanoate (11.6 g) in ether (50 ml) was added dropwise to a mixture of lithium aluminum hydride (1.3 g) and ether (250 ml). The mixture was stirred for 15 minutes at room temperature. To the reaction mixture was added dropwise a saturated aqueous saline solution (5 ml). Insolubles were filtered off, and the filtrate was concentrated under reduced pressure to give 7-(4-benzyloxyphenyl)heptanol (8.5 g, 83%). Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 72-73°C.

Reference Example 57

Methanesulfonyl chloride (8.4 g) was added dropwise to an ice-cooled mixture of 7-(4-benzyloxyphenyl)heptanol (8.4 g), triethylamine (2.8 g) and ethyl acetate (100 ml), followed by stirring for 30 minutes at the same temperature. The reaction mixture was washed with water, dried ($MgSO_4$) and, then,

concentrated to give 7-(4-benzyloxyphenyl)heptyl methanesulfonate (9.9 g, 94%).

NMR(δ ppm in $CDCl_3$): 1.20-1.83(10H,m), 2.54(2H,t,J=7.8Hz), 3.00(3H,s), 4.22(2H,t,J=6.6Hz), 5.04(2H,s), 6.90(2H,d,J=8.6Hz), 7.09(2H,d,J=8.6Hz), 7.25-7.50(5H,m).

Reference Example 58

A mixture of 7-(4-benzyloxyphenyl)heptyl methanesulfonate (9.9 g), sodium cyanide (1.9 g) and N,N-dimethylformamide (DMF) (50 ml) was stirred for 2 hours at 80°C. The reaction mixture was poured into water (300 ml). The resulting crystalline precipitate was collected by filtration, which was recrystallized from ethyl acetate - hexane to give 8-(4-benzyloxyphenyl)octanenitrile (7.3 g, 90%) as colorless prisms, m.p. 49-50°C.

Reference Example 59

A mixture of 8-(4-benzyloxyphenyl)octanenitrile (7.2 g), 4N potassium hydroxide (35 ml) and 2-methoxyethanol (35 ml) was stirred for 20 hours under reflux. The reaction mixture was poured into water (100 ml), which was acidified with 2N hydrochloric acid, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and, then concentrated to give 8-(4-benzyloxyphenyl)octanoic acid (6.7 g, 88%) as colorless prisms, m.p. 95-96°C.

Reference Example 60

In substantially the same manner as in Reference Example 54, 8-(4-benzyloxyphenyl)octanoic acid was subjected to esterification to give ethyl 8-(4-benzyloxyphenyl)octanoate.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7.2Hz), 1.30-1.40(6H,m), 1.45-1.55(4H,m), 2.28(2H,t,J=7.4Hz), 2.54(2H,t,J=8.0Hz), 4.12(2H,q,J=7.2Hz), 5.04(2H,s), 6.89(2H,d,J=8.8Hz), 7.08(2H,d,J=8.8Hz), 7.25-

7.50(5H,m).

Reference Example 61

In substantially the same manner as in Reference Example 12, starting from ethyl 8-(4-benzyloxyphenyl)octanoate, ethyl 9-(4-benzyloxyphenyl)-2-hydroxynonanoate was obtained.

NMR(δ ppm in $CDCl_3$): 1.30(3H,t,J=7.0Hz), 1.31-1.90(12H,m), 2.54(2H,t,J=7.6Hz), 2.72(1H,d,J=6.0Hz), 4.16(1H,s), 4.24(2H,q,J=7.0Hz), 5.04(2H,s), 6.89(2H,d,J=8.8Hz), 7.09(2H,d,J=8.8Hz), 7.28-7.50(5H,m).

Reference Example 62

In substantially the same manner as in Reference Example 9, 4-benzyloxy-3-ethoxybenzaldehyde was allowed to react with triethyl 4-phosphonocrotonate to give ethyl (E,E)-5-(4-benzyloxy-3-ethoxyphenyl)-2,4-pentadienoate. Recrystallization from isopropyl ether gave colorless needles, m.p. 72.5-73.5°C.

Reference Example 63

In substantially the same manner as in Reference Example 10, ethyl (E,E)-5-(4-benzyloxy-3-ethoxyphenyl)-2,4-pentadienoate was subjected to catalytic reduction to give ethyl 5-(3-ethoxy-4-hydroxyphenyl)pentanoate.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7.0Hz), 1.43(3H,t,J=7.0Hz), 1.50-1.76(4H,m), 2.31(2H,t,J=7.1Hz), 2.54(2H,d,J=7.1Hz), 4.10(2H,q,J=7.0Hz), 4.12(2H,q,J=7.0Hz), 5.52(1H,s), 6.66(1H,d,J=8.4Hz), 6.66(1H,s), 6.83(1H,d,J=8.4Hz).

Reference Example 64

In substantially the same manner as in Reference Example 34, ethyl 5-(3-ethoxy-4-hydroxyphenyl)pentanoate was allowed to react with benzyl bromide to give ethyl 5-(4-benzyloxy-3-ethoxyphenyl)pentanoate.

NMR(δ ppm in $CDCl_3$): 1.24(3H,t,J=7.0Hz), 1.45(3H,t,J=7.0Hz), 1.53-1.73(4H,m),

2.31(2H,t,J=7.1Hz), 2.55(2H,t,J=7.2Hz), 4.10(2H,q,J=7.0Hz), 4.12(2H,q,J=7.0Hz), 5.11(2H,s), 6.64(1H,dd,J=8.1&1.9Hz), 6.73(1H,d,J=1.9Hz), 6.81(1H,d,J=8.1Hz), 7.23-7.49(5H,m).

Reference Example 65

In substantially the same manner as in Reference Example 12, starting from ethyl 5-(4-benzyloxy-3-ethoxyphenyl)pentanoate, ethyl 6-(4-benzyloxy-3-ethoxyphenyl)-2-hydroxyhexanoate was obtained.

NMR(δ ppm in $CDCl_3$): 1.31(3H,t,J=7.1Hz), 1.45(3H,t,J=7.1Hz), 1.37-1.92(6H,m), 2.54(2H,t,J=7.3Hz), 2.71(1H,d,J=5.6Hz), 4.10(2H,q,J=7.1Hz), 4.23(2H,q,J=7.1Hz), 4.04-4.29(1H,m), 5.11(2H,s), 6.64(1H,dd,J=8.0&1.8Hz), 6.73(1H,d,J=1.8Hz), 6.81(1H,d,J=8.0Hz), 7.27-7.49(5H,m).

Reference Example 66

In substantially the same manner as in Reference Example 9, 3-benzyloxy-4-methoxybenzaldehyde was allowed to react with triethyl 4-phosphonocrotonate to give ethyl (E,E)-5-(3-benzyloxy-4-methoxyphenyl)-2,4-pentadienoate, m.p. 99-100°C.

Reference Example 67

In substantially the same manner as in Reference Example 10, ethyl (E,E)-5-(3-benzyloxy-4-methoxyphenyl)-2,4-pentadienoate was subjected to catalytic reduction to give ethyl 5-(3-hydroxy-4-methoxyphenyl)pentanoate.

NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7.2Hz), 1.54-1.74(4H,m), 2.31(2H,t,J=7.2Hz), 2.54(2H,d,J=7.2Hz), 3.86(3H,s), 4.12(2H,q,J=7.2Hz), 5.56(1H,s), 6.64(1H,dd,J=8.2&2.0Hz), 6.76(1H,d,J=2.0Hz), 6.77(1H,d,J=8.2Hz).

Reference Example 68

In substantially the same manner as in Reference Example 34, ethyl 5-(3-hydroxy-4-

methoxyphenyl)pentanoate was allowed to react with benzyl bromide to give ethyl 5-(3-benzyloxy-4-methoxyphenyl)pentanoate.
NMR(δ ppm in $CDCl_3$): 1.25(3H,t,J=7.2Hz), 1.47-1.68(4H,m), 2.28(2H,t,J=6.7Hz), 2.52(2H,t,J=6.7Hz), 3.86(3H,s), 4.12(2H,q,J=7.2Hz), 5.14(2H,s), 6.70-6.84(3H,s), 7.29-7.47(5H,m).

Reference Example 69

In substantially the same manner as in Reference Example 12, starting from ethyl 5-(3-benzyloxy-4-methoxyphenyl)pentanoate, ethyl 6-(3-benzyloxy-4-methoxyphenyl)-2-hydroxyhexanoate was obtained.
NMR(δ ppm in $CDCl_3$): 1.28(3H,t,J=7.2Hz), 1.35-1.87(6H,m), 2.51(2H,t,J=7.4Hz), 2.70(1H,d,J=5.8Hz), 3.86(3H,s), 4.06-4.17(1H,m), 4.23(2H,q,J=7.2Hz), 5.13(2H,s), 6.69-6.84(3H,m), 7.29-7.48(5H,m).

Reference Example 70

In substantially the same manner as in Reference Example 1, 3,4-dihydro-2-naphthalenecarboxamide was allowed to react with 1,3-dichloroacetone to give 4-chloromethyl-2-(3,4-dihydro-2-naphthyl)oxazole. Recrystallization from isopropyl ether gave colorless prisms, m.p. 73-74°C.

Working Example 1

A mixture of 5-[3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione (0.35 g), 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (0.265 g), potassium carbonate (0.145 g) and N,N-dimethylformamide (DMF) (10 ml) was stirred for 4 hours at 90-100°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and, then, concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with acetone-hexane (1:3, v/v), 5-[3-[4-(5-

methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.38 g, 75%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 125-126°C.

Working Example 2

In substantially the same manner as in Working Example 1, 5-[3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-phenyloxazole to give 5-[3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-3-(2-phenyl-4-oxazolylmethyl)-2,4-oxazolidinedione. Recrystallization from acetone - isopropyl ether gave colorless needles, m.p. 115-116°C.

Working Example 3

A mixture of 4-isopropoxy-3-methoxycinnamaldehyde (15.68 g), 2,4-oxazolidinedione (21.58 g), piperidine (6.0 g) and acetic acid (450 ml) was stirred for 15 hours under reflux. The reaction mixture was concentrated under reduced pressure. To the concentrate was poured water, which was neutralized with potassium carbonate, followed by extraction with chloroform. The chloroform layer was washed with water and dried ($MgSO_4$), which was then concentrated under reduced pressure. Resulting crystalline precipitates were collected by filtration with ethyl acetate - ether. The filtrate was concentrated under reduced pressure, which was subjected to a silica gel column chromatography. From the fraction eluted with chloroform - ethyl acetate (4:1, v/v), crystals were further obtained. The crystals were combined with those obtained previously to give 5-[3-(4-isopropoxy-3-methoxyphenyl)propenylidene]-2,4-oxazolidinedione (7.6 g, 35%), Recrystallization from ethyl acetate - hexane gave yellow prisms, m.p. 226-227°C.

Working Example 4

5-[3-(4-isopropoxy-3-methoxyphenyl)propenylidene]-2,4-oxazolidinedione (7.1 g) was dissolved in tetrahydrofuran (THF) (150 ml). To the solution was added palladium-carbon (5%, 7.1 g), which was subjected to catalytic reduction at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with chloroform - ethyl acetate (4:1, v/v), 5-[3-(4-isopropoxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione (4.29 g, 60%) was obtained as an oily product.
NMR(δ ppm in $CDCl_3$): 1.35(6H,d,J=6Hz), 1.79-2.05(4H,m), 2.62(2H,t,J=7Hz), 3.84(3H,s), 4.47(1H,m), 4.84(1H,dd,J=7&5Hz), 6.67(1H,dd,J=8&2Hz), 6.69(1H,s), 6.82(1H,d,J=8Hz), 8.33(1H,s).

Working Example 5

A solution of titanium tetrachloride ($TiCl_4$) (10.6 g) in dichloromethane (10 ml) was added dropwise, at 0°C, to a solution of 5-[3-(4-isopropoxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione (4.3 g) in dichloromethane (130 ml). The mixture was stirred for one hour at 0°C, which was poured into 2N HCl. The mixture was stirred for 15 minutes at room temperature. The organic layer was separated, and the aqueous layer was subjected to extraction with chloroform. The chloroform layer was combined with the organic layer separated previously, which was washed with water, 2N HCl and water, successively, followed by drying ($MgSO_4$) and concentration to give 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione (2.8 g, 76%). Recrystallization from ethanol-hexane gave colorless prisms, m.p. 147-148°C

Working Example 6

Sodium hydride (60% oil, 0.32 g) was added, at 0

°C, a solution of 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione (1.0 g) in N,N-dimethylformamide (DMF) (20 ml). The mixture was stirred for one hour at room temperature. To the reaction mixture was then added 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (0.87 g). The mixture was stirred for 3.5 hours at 90°C. The reaction mixture was poured into water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to give 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (1.1 g, 66%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 178-179°C

Working Example 7

In substantially the same manner as in Working Example 1, 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from acetone - isopropyl ether gave colorless needles, m.p. 123-124°C.

Working Example 8

In substantially the same manner as in Working Example 1, 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-thiazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 134-135°C.

Working Example 9

In substantially the same manner as in Working Example 1, 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-phenyloxazole to give 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-phenyl-4-oxazolylmethyl)-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 155-156°C.

Working Example 10

Sodium hydride (60% oil, 0.34 g) was added, at 0°C, to a solution of 5-[4-(4-hydroxyphenyl)butyl]-2,4-oxazolidinedione (1.0 g) in N,N-dimethylformamide (DMF) (20 ml). The mixture was stirred for one hour at room temperature. To the reaction mixture was then added 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (0.93 g), which was stirred for 3.5 hours at 90°C. The reaction mixture was poured into water, which was neutralized with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then, concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - chloroform (1:5, v/v), 5-[4-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione (0.29 g, 17%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 144-145°C.

Working Example 11

In the column chromatography of Working Example 10, from the fraction subsequently eluted, 5-[4-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.15 g, 12%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless plates, m.p. 162-163°C

Working Example 12

In substantially the same manner as in Working Example 10, 5-[4-(4-hydroxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[4-[4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione. Recrystallization from chloroform - ethyl acetate gave colorless needles, m.p. 166-167°C.

Working Example 13

In the column chromatography of Working Example 12, from the fraction subsequently eluted, 5-[4-[4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-phenylethenyl]-4-thiazolylmethyl]-2,4-oxazolidinedione was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 118-119°C

Working Example 14

Sodium hydride (60% oil, 0.13 g) was added, at room temperature, to a solution of 5-[4-(4-hydroxyphenyl)butyl]-2,4-oxazolidinedione (0.35 g) in N,N-dimethylformamide (DMF) (8 ml). The mixture was stirred for 10 minutes, to which was then added 4-chloromethyl-2-[(E)-2-(2-furyl)ethenyl]oxazole (0.6 g). The mixture was stirred for 1.5 hour at 90°C. The reaction mixture was poured into water, which was neutralized with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - chloroform (1:5, v/v), 5-[4-[4-[2-[(E)-2-(2-furyl)ethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[2-[(E)-(2-furyl)ethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.38 g, 46%) was obtained. Recrystallization from

ethyl acetate - hexane gave colorless prisms, m.p. 146-147°C.

Working Example 15

Sodium hydride (60% oil, 0.067 g) was added, at room temperature, to a solution of 5-[5-(4-hydroxyphenyl)pentyl]-2,4-oxazolidinedione (0.20 g) in N,N-dimethylformamide (DMF) (8 ml). The mixture was stirred for 25 minutes, to which was then added 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (0.4 g). The mixture was stirred for one hour at 85°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then, concentrated under reduced pressure. The residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - chloroform (1:10, v/v), 5-[5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]pentyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.25 g, 52%) was obtained. Recrystallization from acetone-ethanol gave colorless needles, m.p. 125-126°C.

Working Example 16

In substantially the same manner as in Working Example 15, 5-[6-(4-hydroxyphenyl)hexyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[6-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]hexyl-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from acetone-ethanol gave colorless prisms, m.p. 149-150°C.

Working Example 17

Sodium hydride (60% oil, 0.065 g) was added at room temperature to a solution of 5-[6-(4-benzyloxyphenyl)hexyl]-2,4-oxazolidinedione (0.50 g) in

N,N-dimethylformamide (DMF) (10 ml). The mixture was stirred for 25 minutes, to which was then added 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (0.354 g), followed by stirring for 1.5 hour at 90°C. The reaction mixture was poured into water, which was neutralized with 2N HCl and subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then, concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - chloroform (1:5, v/v), 5-[6-(4-benzyloxyphenyl)hexyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.445 g, 59%) was obtained. Recrystallization from acetone-ethanol gave colorless prisms, m.p. 103-104°C.

Working Example 18

A mixture of 4-isopropoxy-3-methoxycinnamaldehyde (7.85 g), 2,4-thiazolidinedione (8.35 g), piperidine (3.03 g) and acetic acid (260 ml) was stirred for 5 hours under reflux. The reaction mixture was poured into water (100 ml). Resulting crystalline precipitate was collected by filtration and dissolved in chloroform (500 ml). The solution was washed with water, dried ($MgSO_4$) and, then concentrated under reduced pressure to give 5-[3-(4-isopropoxy-3-methoxyphenyl)propenylidene]-2,4-thiazolidinedione (6.95 g, 61%). Recrystallization from ethyl acetate-hexane gave yellow prisms, m.p. 230-231°C.

Working Example 19

To a mixture of 5-[3-(4-isopropoxy-3-methoxyphenyl)propenylidene]-2,4-thiazolidinedione (6.45 g) and tetrahydrofuran (THF) (550 ml) was added palladium-carbon (5%, 17.0 g), which was subjected to catalytic reduction at room temperature under hydrogen pressure of 3 kgf/cm^2. The catalyst was filtered off, and the filtrate was concentrated under reduced

pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with chloroform - ethyl acetate (4:1, v/v), 5-[3-(4-isopropoxy-3-methoxyphenyl)propyl]-2,4-thiazolidinedione (4.9 g, 75%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.35(6H,d,J=6Hz), 1.67-2.19(4H,m), 2.62(2H,t,J=7Hz), 3.85(3H,s), 4.28(1H,dd,J=8&4Hz), 4.47(1H,m), 6.67(1H,dd,J=8&2Hz), 6.69(1H,s), 6.83(1H,d,J=8Hz), 8.45(1H,s).

Working Example 20

In substantially the same manner as in Working Example 5, 5-[3-(4-isopropoxy-3-methoxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with titanium tetrachloride to give 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-thiazolidinedione as an oily product.

NMR(δ ppm in $CDCl_3$): 1.69-2.17(4H,m), 2.61(2H,t,J=7Hz), 3.89(3H,s), 4.28(1H,dd,J=9&4Hz), 5.51(1H,s), 6.66(1H,dd,J=9&2Hz), 6.66(1H,d,J=2Hz), 6.84(1H,d,J=9Hz), 8.37(1H,s).

Working Example 21

In substantially the same manner as in Working Example 15, 5-[3-(4-hydroxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-thiazolidinedione. Recrystallization from acetone-ethanol gave colorless prisms, m.p. 114-115°C

Working Example 22

In substantially the same manner as in Working Example 14, 5-[3-(4-hydroxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-(2-furyl)ethenyl]oxazole to give 5-[3-[4-[2-[(E)-2-(2-furyl)ethenyl]-4-

oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-(2-furyl)ethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 162-163°C.

Working Example 23

In substantially the same manner as in Working Example 14, 5-[3-(4-hydroxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E,E)-4-phenyl-1,3-butadienyl]oxazole to give 5-[3-[4-[2-[(E,E)-4-phenyl-1,3-butadienyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E,E)-4-phenyl-1,3-butadienyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 168-169°C

Working Example 24

In substantially the same manner as in Working Example 1, 5-[3-[4-[2-[(E)-2-phenylethenyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-(2-furyl)ethenyl]oxazole to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-(2-furyl)ethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 157-158°C.

Working Example 25

In substantially the same manner as in Working Example 1, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with ethyl bromoacetate to give 3-ethoxycarbonylmethyl-5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 93-94°C.

Working Example 26

4-(4-Benzyloxyphenyl)-2-ethoxycarbonyloxybutan amide (1.0 g) was dissolved in tetrahydrofuran (THF)

(30 ml). To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.85 g). The mixture was stirred for 4 hours at room temperature, then for 12 hours under reflux. The reaction mixture was poured into water, which was acidified with 1N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then, concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:2, v/v), 5-[2-(4-benzyloxyphenyl)ethyl]-2,4-oxazolidinedione (0.36 g, 41%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 145-146°C

Working Example 27

5-[2-(4-Benzyloxyphenyl)ethyl]-2,4-oxazolidinedione (21.8 g) was suspended in tetrahydrofuran (THF) (500 ml), to which was added palladium-carbon (5%, 21.8 g). The mixture was subjected to catalytic reduction at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 5-[2-(4-hydroxyphenyl)ethyl]-2,4-oxazolidinedione (9.45 g, 61%). Recrystallization from methanol gave colorless prisms, m.p. 174-175°C

Working Example 28

In substantially the same manner as in Working Example 14, 5-[2-(4-hydroxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[2-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 185-186°C.

Working Example 29

A mixture of ethyl 8-(4-benzyloxyphenyl)-2-hydroxyoctanoate (14.0 g), potassium cyanate (KCNO) (15.3 g) and butanol (200 ml) was stirred for 4 days under reflux. The reaction mixture was concentrated under reduced pressure, which was acidified with 1N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - chloroform (1:4, v/v), 5-[6-(4-benzyloxyphenyl)hexyl]-2,4-oxazolidinedione (10.2 g, 73%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 137-138°C.

Working Example 30

In tetrahydrofuran (THF) (100 ml) was suspended 5-[6-(4-benzyloxyphenyl)hexyl]-2,4-oxazolidinedione (8.0 g). To the suspension was added palladium-carbon (5%, 2.0 g). The mixture was subjected to catalytic reduction at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 5-[6-(4-hydroxyphenyl)hexyl]-2,4-oxazolidinedione (5.9 g, 98%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 151-152°C.

Working Example 31

In substantially the same manner as in Working Example 29, ethyl 6-(4-benzyloxyphenyl)-2-hydroxyhexanoate was allowed to react with potassium cyanate (KCNO) to give 5-[4-(4-benzyloxyphenyl)butyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 144-145°C.

Working Example 32

In substantially the same manner as in Working Example 30, 5-[4-(4-benzyloxyphenyl)butyl]-2,4-oxazolidinedione was subjected to catalytic reduction

to give 5-[4-(4-hydroxyphenyl)butyl]-2,4-oxazolidinedione.

Working Example 33

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-thiazolidinedione. Recrystallization from chloroform-ethanol gave pale orange prisms, m.p. 154-155°C.

Working Example 34

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]propyl]-2,4-thiazolidinedione. Recrystallization from chloroform-ethanol gave pale orange prisms, m.p. 161-162°C.

Working Example 35

A mixture of 5-[3-(4-hydroxyphenyl)propyl]-2,4-oxazolidinedione (0.30 g), 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (0.28 g), potassium carbonate (0.18 g) and N,N-dimethylformamide (DMF) (20 ml) was stirred for 3 hours at temperatures ranging from 85 to 90°C. The reaction mixture was poured into water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then, concentrated under reduced pressure. The concentrate was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (2:3, v/v), 5-[3-(4-hydroxyphenyl)propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.28 g, 52%) was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 1.6-2.15(4H,m), 2.58(2H,t,J=7Hz), 4.66(2H,s), 4.80(1H,dd,J=6.5&4.5Hz), 4.94(1H,br s), 6.72(2H,d,J=8.5Hz), 6.88(1H,d,J=16.5Hz), 7.00(2H,d,J=8.5Hz), 7.3-7.55(6H,m), 7.64(1H,s).

Working Example 36

A mixture of 5-[3-(4-hydroxyphenyl)propyl]-2,4-oxazolidinedione (0.50 g), 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole (1.03 g), potassium carbonate (0.65 g) and N,N-dimethylformamide (DMF) (20 ml) was stirred for 12 hours at temperatures ranging from 85 to 90°C. The reaction mixture was poured into water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and, then concentrated under reduced pressure to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione (0.75 g, 59%). Recrystallization from acetone-methanol gave colorless needles, m.p. 166-167°C.

Working Example 37

A mixture of 4-isopropoxycinnamaldehyde (6.0 g), 2,4-thiazolidinedione (5.54 g), piperidine (2.69 g) and acetic acid (30 ml) was stirred for 5 hours under reflux. The reaction mixture was concentrated under reduced pressure. The resulting crystalline precipitate (4.40 g), 5-(4-isopropoxycinnamylidene)-2,4-thiazolidinedione, was collected by filtration, which was washed with ethyl acetate. The crystalline product was dissolved in tetrahydrofuran (THF) (100 ml), to which was added palladium-carbon (5%, 2.20 g). The mixture was subjected to catalytic reduction at room temperature under hydrogen pressure of 3.8 kgf/cm^2. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was subjected to a silica gel column

chromatography. From the fraction eluted with chloroform - ethyl acetate (9:1, v/v), 5-[3-(4-isopropoxyphenyl)propyl]-2,4-thiazolidinedione (3.61 g, 39%) was obtained as an oily product.
NMR(δ ppm in $CDCl_3$): 1.32(6H,d,J=6Hz), 1.6-2.3(4H,m), 2.61(2H,t,J=7.5Hz), 4.28(1H,dd,J=8.5&4.5Hz), 4.4-4.65(1H,m), 6.82(1H,m), 6.82(2H,d,J=8.5Hz), 7.06(2H,d,J=8.5Hz), 8.34(1H,br s).

Working Example 38

In substantially the same manner as in Working Example 5, 5-[3-(4-isopropoxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with titanium tetrachloride to give 5-[3-(4-hydroxyphenyl)propyl]-2,4-thiazolidinedione. Recrystallization from acetone - isopropyl ether gave colorless prisms, m.p. 129-130°C.

Working Example 39

In substantially the same manner as in Working Example 6, 5-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-phenyloxazole to give 5-[2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-methoxyphenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - chloroform gave colorless prisms, m.p. 194-195°C.

Working Example 40

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-bromoacetyl-5-methyl-2-phenyloxazole to give 5-[3-[3-methoxy-4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxo-ethoxy]phenyl]propyl]-2,4-oxazolidinedione as an oily product.
NMR(δ ppm in $CDCl_3$): 1.7-2.15(4H,m), 2.63(2H,t,J=7Hz), 2.73(3H,s), 3.91(3H,s), 4.85(1H,dd,J=6.5&5Hz), 5.43(2H,s), 6.65(1H,dd,J=8&2Hz), 6.73(1H,d,J=2Hz),

6.79(1H,d,J=8Hz), 7.45-7.55(3H,m), 7.95(1H,br s), 8.0-8.1(2H,m).

Working Example 41

Sodium borohydride (0.045 g) was added, at room temperature in limited amounts, to a solution of 5-[3-[3-methoxy-4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxo-ethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.37 g) in tetrahydrofuran (THF) (5 ml) - ethanol (5 ml). The mixture was stirred for further two hours at room temperature. The reaction mixture was poured into water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$) and, then, the solvent was distilled off. The oily residue was subjected to a silica gel column chromatography. From the fraction eluted with chloroform-methanol (100:1, v/v), 5-[3-[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione (0.31 g, 83%). Recrystallization from acetone - isopropyl ether gave colorless prisms, m.p. 151-152°C.

Working Example 42

In substantially the same manner as in Working Example 3, 3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamaldehyde was condensed with 2,4-oxazolidinedione. The condensate was subjected to catalytic reduction to give 5-[3-[3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-2,4-oxazolidinedione.

NMR(δ ppm in $CDCl_3$): 1.73(3H,d,J=6.5Hz), 1.7-2.1(4H,m), 2.28(3H,s), 2.59(2H,t,J=7Hz), 3.85(3H,s), 4.82(1H,dd,J=7&4.5Hz), 5.32(1H,q,J=6.5Hz), 6.59(1H,dd,J=8&2Hz), 6.68(1H,d,J=2Hz), 6.78(1H,d,J=8Hz), 7.35-7.5(3H,m), 7.95-8.1(2H,m), 8.66(1H,br s).

Working Example 43

A mixture of 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.64 g), palladium-carbon (5%, 1.3 g) and tetrahydrofuran (THF) (35 ml) was subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated to give 5-[3-[3-methoxy-4-[2-(2-phenylethyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.43 g, 67%). Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 122-123°C.

Working Example 44

In substantially the same manner as in Working Example 43, 5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was subjected to catalytic hydrogenation at room temperature under atmospheric pressure to give 5-[3-[3-methoxy-4-[2-(2-phenylethyl)-4-thiazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 136-137°C.

Working Example 45

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-phenylthiazole to give 5-[3-[3-methoxy-4-(5-methyl-2-phenyl-4-thiazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 128-129°C.

Working Example 46

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 5-chloromethyl-3-phenyl-1,2,4-oxadiazole to give 5-[3-[3-methoxy-4-(3-phenyl-1,2,4-oxadiazol-5-

ylmethoxy)phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 110-111°C.

Working Example 47

A mixture of ethyl 6-(4-benzyloxy-3-methoxyphenyl)-2-hydroxyhexanoate (15.22 g), potassium cyanate (KCNO) (13.26 g) and butanol (180 ml) was stirred for 72 hours under reflux. The reaction mixture was concentrated under reduced pressure, which was poured into water and acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), and, then, the solvent was distilled off to give an oily product, which was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:1, v/v), 5-[4-(4-benzyloxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione (11.22 g, 74%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 92-93°C.

Working Example 48

In substantially the same manner as in Working Example 6, 5-[4-(4-hydroxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 171-172°C.

Working Example 49

In substantially the same manner as in Working Example 6, 5-[4-(4-hydroxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[4-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave

colorless prisms, m.p. 167-168°C

Working Example 50

In substantially the same manner as in Working Example 47, ethyl 4-(4-benzyloxy-3-ethoxyphenyl)-2-hydroxybutanoate was allowed to react with potassium cyanate (KCNO) to give 5-[2-(4-benzyloxy-3-ethoxyphenyl)ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 143-144°C.

Working Example 51

In substantially the same manner as in Working Example 47, ethyl 4-(3-benzyloxy-4-methoxyphenyl)-2-hydroxybutanoate was allowed to react with potassium cyanate (KCNO) to give 5-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione as an oily product.

NMR(δ ppm in $CDCl_3$): 1.95-2.25(2H,m), 2.59-2.84(2H,m), 3.87(3H,s), 4.58(1H,dd,J=8.2&4.8Hz), 5.15(2H,s), 6.72-6.86(3H,m), 7.26-7.45(5H,m), 8.52(1H,br s).

Working Example 52

In substantially the same manner as in Working Example 6, 5-[4-(4-hydroxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-(2-naphthyl)ethenyl]oxazole to give 5-[4-[3-methoxy-4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 169-170°C.

Working Example 53

In substantially the same manner as in Working Example 3, 4-benzyloxy-3,5-dimethoxycinnamaldehyde was subjected to condensation with 2,4-oxazolidinedione to give 5-(4-benzyloxy-3,5-dimethoxycinnamylidene)-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave yellow prisms, m.p. 181-182°C.

Working Example 54

In substantially the same manner as in Working Example 4, 5-(4-benzyloxy-3,5-dimethoxycinnamylidene)-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[3-(4-hydroxy-3,5-dimethoxyphenyl)propyl]-2,4-oxazolidinedione. Recrystallization from ethanol-hexane gave colorless prisms, m.p. 155-156°C.

Working Example 55

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3,5-dimethoxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[3,5-dimethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 94-95°C.

Working Example 56

A mixture of ethyl 2-hydroxy-4-(4-hydroxy-3-methoxyphenyl)butanoate (0.73 g), potassium cyanate (KCNO) (0.7 g) and butanol (25 ml) was stirred for 18 hours under reflux. The reaction mixture was concentrated under reduced pressure, which was poured into water and acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was distilled off, and the oily residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - chloroform (1:4, v/v), 5-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-2,4-oxazolidinedione (0.2 g, 28%) was obtained.

NMR(δ ppm in $CDCl_3$): 2.12-2.16(2H,m), 2.73-2.83(2H,m), 3.89(3H,s), 4.80(1H,dd,J=8&5Hz), 5.53(1H,s), 6.70(1H,d,J=2Hz), 6.72(1H,dd,J=7&2Hz), 6.86(1H,d,J=9Hz), 8.21(1H,br s).

Working Example 57

In substantially the same manner as in Working

Example 4, 5-[4-(4-benzyloxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[4-(4-hydroxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 115-116°C

Working Example 58

In substantially the same manner as in Working Example 4, 5-[2-(4-benzyloxy-3-ethoxyphenyl)ethyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[2-(4-hydroxy-3-ethoxyphenyl)ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 154.5-155°C.

Working Example 59

In substantially the same manner as in Working Example 4, 5-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione. Recrystallization from isopropyl ether - hexane gave colorless prisms, m.p. 121-122°C.

Working Example 60

1-Dodecanethiol (2.37 g) was added, at 0 °C, to a suspension of aluminum chloride (1.56 g) in dichloromethane (30 ml). The mixture was stirred for 10 minutes, to which was then added dropwise, at the same temperature, a solution of 5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione (0.5 g) in dichloromethane (10 ml). The reaction mixture was stirred for 2 hours at room temperature, which was then poured into ice-water, followed by extraction with dichloromethane. The dichloromethane layer was washed with water and dried ($MgSO_4$). The solvent was then distilled off, and the residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with

ethyl acetate - chloroform (1:3, v/v), 5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-hydroxyphenyl]propyl]-2,4-oxazolidinedione (0.21 g, 43%) was obtained. Recrystallization from dichloromethane-methanol gave colorless prisms, m.p. 152-153°C.

Working Example 61

In substantially the same manner as in Working Example 15, 5-(4-hydroxybenzyl)-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from acetone gave colorless crystals, m.p. 159-160°C.

Working Example 62

In substantially the same manner as in Working Example 15, 5-(4-hydroxybenzyl)-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]benzyl]-3-[2-[(E)-2-phenylethenyl]-4-thiazolylmethyl]-2,4-oxazolidinedione. Recrystallization from acetone gave colorless crystals, m.p. 153-155°C.

Working Example 63

In substantially the same manner as in Working Example 17, 5-(4-benzyloxybenzyl)-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-(4-benzyloxybenzyl)-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless crystals, m.p. 134-135°C.

Working Example 64

In substantially the same manner as in Working Example 43, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was

subjected to catalytic reduction to give 5-[3-[4-[2-(2-phenylethyl)-4-oxazolylmethoxy]phenyl]propyl]-3-[2-(2-phenylethyl)-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 113-114°C.

Working Example 65

In substantially the same manner as in Working Example 15, 5-[2-(4-hydroxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E,E)-4-phenyl-1,3-butadienyl]oxazole to give 5-[2-[4-[2-[(E,E)-4-phenyl-1,3-butadienyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[2-[(E,E)-4-phenyl-1,3-butadienyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from tetrahydrofuran-ethanol gave colorless prisms, m.p. 196-197°C.

Working Example 66

A mixture of 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.30 g), 4-(2-chloroethyl)morpholine hydrochloride (0.15 g), potassium carbonate (0.22 g) and N,N-dimethylformamide (DMF) (10 ml) was stirred for 5 hours at 100°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was then distilled off, and the residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with chloroform - ethyl acetate (4:1, v/v), 3-(2-morpholinoethyl)-5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.14 g, 37%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 105-106°C.

Working Example 67

In substantially the same manner as in Working Example 66, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-

oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethylpyridine hydrochloride to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(4-pyridylmethyl)-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 151-152°C.

Working Example 68

In substantially the same manner as in Working Example 6, 5-[2-(4-hydroxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[2-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from ethanol gave colorless prisms, m.p. 156-158°C.

Working Example 69

In substantially the same manner as in Working Example 15, 5-[3-(4-hydroxy-3-methoxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[3-[3-methoxy-4-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from chloroform-methanol gave colorless prisms, m.p. 202-203°C.

Working Example 70

In substantially the same manner as in Working Example 1, 5-(2,4,5-triisopropoxybenzyl)-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-5-(2,4,5-triisopropoxybenzyl)-2,4-thiazolidinedione. Recrystallization from isopropyl ether gave colorless prisms, m.p. 100-101°C.

Working Example 71

In substantially the same manner as in Working Example 15, 5-(4-hydroxybenzyl)-2,4-thiazolidinedione

was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-thiazolidinedione. Recrystallization from acetone-ethanol gave colorless prisms, m.p. 165-166 °C.

Working Example 72

In substantially the same manner as in Working Example 15, 5-[4-(4-hydroxyphenyl)butyl]-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 134-135°C.

Working Example 73

In substantially the same manner as in Working Example 15, 5-[5-(4-hydroxyphenyl)pentyl]-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]pentyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 98-99°C.

Working Example 74

In substantially the same manner as in Working Example 6, 5-[6-(4-hydroxyphenyl)hexyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[6-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]hexyl]-2,4-oxazolidinedione. Recrystallization from ethanol gave colorless prisms, m.p. 136-137°C.

Working Example 75

In substantially the same manner as in Working Example 15, 5-[4-(4-hydroxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]thiazole to give 5-[4-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-thiazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-phenylethenyl]-4-thiazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 108-109°C.

Working Example 76

In substantially the same manner as in Working Example 1, 5-[3-[4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from acetone - isopropyl ether gave colorless prisms, m.p. 150-151°C.

Working Example 77

In substantially the same manner as in Working Example 1, 5-[3-[4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 1-bromodecane to give 3-decyl-5-[3-[4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from acetone - isopropyl ether gave colorless prisms, m.p. 116-117°C.

Working Example 78

In substantially the same manner as in Working Example 1, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 1-bromodecane to give 3-decyl-5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave

colorless prisms, m.p. 103-104°C.

Working Example 79

To a solution of 4-(2-chloroethyl)morpholine hydrochloride (0.32 g) in water (1 ml) was added potassium carbonate (0.24 g). The mixture was subjected to extraction with toluene. The toluene layer was dried ($MgSO_4$), to which were added 5-[3-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione (0.50 g) and potassium carbonate (0.24 g). The mixture was stirred for 5 hours at temperatures ranging from 90 to 100°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), from which the solvent was distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:1, v/v), 5-[3-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-3-(2-morpholinoethyl)-2,4-oxazolidinedione (0.32 g, 51%) was obtained. Recrystallization from acetone - isopropyl ether gave colorless prisms, m.p. 105-106°C.

Working Example 80

In substantially the same manner as in Working Example 79, 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-oxazolidinedione was allowed to react with 4-(2-chloroethyl)morpholine to give 3-(2-morpholinoethyl)-5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 141-142°C.

Working Example 81

In substantially the same manner as in Working Example 79, 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-oxazolidinedione was allowed to react with 1-(2-chloroethyl)piperidine to

give 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 130-131°C.

Working Example 82

In substantially the same manner as in Working Example 79, 5-[4-[2-[(E)-2-phenylethenyl)-4-oxazolylmethoxy]benzyl]-2,4-oxazolidinedione was allowed to react with N,N-dimethylaminoethyl chloride to give 3-(2-dimethylaminoethyl)-5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 106-107°C.

Working Example 83

In substantially the same manner as in Working Example 47, ethyl 10-(4-benzyloxyphenyl)-2-hydroxydecanoate was allowed to react with potassium cyanate (KCNO) to give 5-[8-(4-benzyloxyphenyl)octyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 148-149°C.

Working Example 84

In substantially the same manner as in Working Example 4, 5-[8-(4-benzyloxyphenyl)octyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[8-(4-hydroxyphenyl)octyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 150-151°C.

Working Example 85

In substantially the same manner as in Working Example 15, 5-[8-(4-hydroxyphenyl)octyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[8-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]octyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave

colorless prisms, m.p. 156-157°C.

Working Example 86

In substantially the same manner as in Working Example 6, 5-[8-(4-hydroxyphenyl)octyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[8-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]octyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 141-142°C.

Working Example 87

In substantially the same manner as in Working Example 79, 5-[2-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 4-(2-chloroethyl)morpholine to give 3-(2-morpholinoethyl)-5-[2-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 122-123°C.

Working Example 88

In substantially the same manner as in Working Example 79, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowded to react with 1-(2-chloroethyl)piperidine to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 103-104°C.

Working Example 89

To a solution of 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.25 g) in N,N-dimethylformamide (DMF) (10 ml) was added at 0°C sodium hydride (60% oil, 0.026 g). The mixture was stirred for one hour, to which was added methyl iodide (0.17 g). The mixture was stirred for one hour at the same temperature, which was poured into

water and acidified, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), and, then, the solvent was distilled off. The residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:2, v/v), 3-methyl-5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.14 g, 54%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 129-130°C.

Working Example 90

In substantially the same manner as in Working Example 89, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with geranyl bromide to give 3-geranyl-5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 97-98°C.

Working Example 91

To a solution of 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione (0.8 g) in methanol (100 ml) was added hydrochloric acid - methanol (10%, 0.58 g). The mixture was stirred for one hour at room temperature. The resulting crystalline precipitate was collected by filtration, which was recrystallized from N,N-dimethylformamide-ether to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione hydrochloride (0.40 g, 47%) as colorless prisms, m.p. 212-213°C.

Working Example 92

In substantially the same manner as in Working Example 15, 5-[2-(4-hydroxyphenyl)ethyl]-2,4-thiazolidinedione was allowed to react with 4-

chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[2-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-thiazolidinedione. Recrystallization from acetone-ethanol gave colorless prisms, m.p. 114-115°C.

Working Example 93

In substantially the same manner as in Working Example 15, 5-[7-(4-hydroxyphenyl)heptyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[7-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]heptyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 120-121°C.

Working Example 94

In substantially the same manner as in Working Example 47, ethyl 9-(4-benzyloxyphenyl)-2-hydroxynonanoate was allowed to react with potassium cyanate (KCNO) to give 5-[7-(4-benzyloxyphenyl)heptyl]-2,4-oxazolidinedione. Recrystallization from ethanol gave colorless prisms, m.p. 93-95°C.

Working Example 95

In substantially the same manner as in Working Example 4, 5-[7-(4-benzyloxyphenyl)heptyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[7-(4-hydroxyphenyl)heptyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 94-95°C.

Working Example 96

In substantially the same manner as in Working Example 3, 4-benzyloxy-3,5-dimethoxycinnamaldehyde was subjected to condensation with 2,4-thiazolidinedione to give 5-(4-benzyloxy-3,5-dimethoxycinnamylidene)-2,4-thiazolidinedione. Recrystallization from chloroform-

ethanol gave yellow prisms, m.p. 217-218°C.

Working Example 97

In substantially the same manner as in Working Example 4, 5-(4-benzyloxy-3,5-dimethoxycinnamylidene)-2,4-thiazolidinedione was subjected to catalytic reduction to give 5-[3-(4-benzyloxy-3,5-dimethoxyphenyl)propyl]-2,4-thiazolidinedione. Recrystallization from ethanol-hexane gave colorless prisms, m.p. 101-102°C.

Working Example 98

In substantially the same manner as in Working Example 5, 5-[3-(4-benzyloxy-3,5-dimethoxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with titanium tetrachloride to give 5-[3-(4-hydroxy-3,5-dimethoxyphenyl)propyl]-2,4-thiazolidinedione as an oily product.

NMR(δ ppm in $CDCl_3$): 1.75-2.12(4H,m), 2.61(2H,t,J=7Hz), 3.88(6H,s), 4.29(1H,dd,J=8&4Hz), 5.42(1H,s), 6.39(2H,s).

Working Example 99

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3,5-dimethoxyphenyl)propyl]-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[3,5-dimethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 163-164°C

Working Example 100

In substantially the same manner as in Working Example 1, 5-[3-[3,5-dimethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[3-[3,5-dimethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-

phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione as an oily product.

NMR(δ ppm in $CDCl_3$): 1.78-1.90(4H,m), 2.62(2H,t,J=7Hz), 3.82(6H,s), 4.66(2H,s), 4.84(1H,dd,J=6&4Hz), 4.99(2H,s), 6.37(2H,s), 6.89(1H,d,J=16Hz), 6.94(1H,d,J=16Hz), 7.33-7.56(12H,m), 7.64(1H,s), 7.69(1H,s).

Working Example 101

In substantially the same manner as in Working Example 15, 5-[4-(4-hydroxy-3-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-(2-naphthyl)ethenyl]oxazole to give 5-[4-[3-methoxy-4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 125-126°C.

Working Example 102

In substantially the same manner as in Working Example 79, 5-[4-[3-methoxy-4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione was allowed to react with 4-(2-chloroethyl)morpholine to give 5-[4-[3-methoxy-4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-(2-morpholinoethyl)-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 118-119°C.

Working Example 103

In substantially the same manner as in Working Example 47, ethyl 6-(4-benzyloxy-3-ethoxyphenyl)-2-hydroxyhexanoate was allowed to react with potassium cyanate (KCNO) to give 5-[4-(4-benzyloxy-3-ethoxyphenyl)butyl]-2,4-oxazolidinedione. Recrystallization from isopropyl ether gave colorless prisms, m.p. 80-81°C.

Working Example 104

In substantially the same manner as in Working Example 4, 5-[4-(4-benzyloxy-3-ethoxyphenyl)butyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[4-(3-ethoxy-4-hydroxyphenyl)butyl]]-2,4-oxazolidinedione as an oily product.

NMR(δ ppm in $CDCl_3$): 1.44(3H,t,J=7.0Hz), 1.47-2.14(6H,m), 2.55(2H,t,J=7.4Hz), 4.10(2H,q,J=7.0Hz), 4.83(1H,dd,J=7.2&4.4Hz), 5.66(1H,br s), 6.64(1H,d,J=8.4Hz), 6.66(1H,s), 6.83(1H,d,J=8.4Hz), 8.45(1H,br s).

Working Example 105

In substantially the same manner as in Working Example 6, 5-[2-(4-hydroxy-3-ethoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - tetrahydrofuran gave colorless prisms, m.p. 175-176°C.

Working Example 106

In substantially the same manner as in Working Example 6, 5-[2-(4-hydroxy-3-ethoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-(2-naphthyl)oxazole to give 5-[2-[3-ethoxy-4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from tetrahydrofuran gave colorless prisms, m.p. 204-205°C.

Working Example 107

To a mixture of 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione (1.35 g), potassium carbonate (0.622 g) and N,N-dimethylformamide (DMF) (10 ml) was added at room temperature 2-iodo ethanol (1.03 g). The mixture was stirred for 2 hours at 50°C. The reaction mixture was poured into water, which was subjected to

extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off to give 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-hydroxyethyl)-2,4-oxazolidinedione (1.15 g, 78%). Recrystallization from ethyl acetate - hexane gave colorless needles, m.p. 120-121°C.

Working Example 108

To a mixture of 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-hydroxyethyl)-2,4-oxazolidinedione (0.985 g), triethylamine (0.304 g) and ethyl acetate (50 ml) was added dropwise, at room temperature, methanesulfonyl chloride (0.344 g). The mixture was stirred for one hour, which was poured into water, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was then distilled off to give an oily substance, which was dissolved in N,N-dimethylformamide (DMF) (10 ml). To this solution was added sodium iodide (0.899 g), which was stirred for 4 hours at 80°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$). The solvent was then distilled off to give 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-iodoethyl)-2,4-oxazolidinedione (0.753 g, 62%). Recrystallization from ethyl acetate gave colorless needles, m.p. 149-150°C.

Working Example 109

To a mixture of 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-iodoethyl)-2,4-oxazolidinedione (0.301 g), potassium carbonate (0.104 g) and N,N-dimethylformamide (DMF) (5 ml) was added 4-methyl piperazine (0.10 g). The mixture was stirred for 16 hours at room temperature.

The reaction mixture was poured into water, which was acidified with 0.1N HCl, followed by washing with ethyl acetate. The aqueous layer was basified with an aqueous solution of sodium hydrogencarbonate, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off, and the residual oily substance was dissolved in ethyl acetate (5 ml). To this solution was added hydrochloric acid - ethanol (10%, 0.8 ml), which was concentrated under reduced pressure. The residual solid substance was recrystallized from ethanol-methanol to give 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[2-(4-methyl-1-piperazinyl)ethyl]-2,4-oxazolidinedione dihydrochloride (0.13 g, 40%) as colorless prisms, m.p. 143-145°C.

Working Example 110

In substantially the same manner as in Working Example 109, 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-iodoethyl)-2,4-oxazolidinedione was allowed to react with 4-piperidinopiperidine to give 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[2-(4-piperidino-1-piperidinyl)ethyl]-2,4-oxazolidinedione dihydrochloride. Recrystallization from ethanol-methanol gave colorless prisms, m.p. 210-212°C.

Working Example 111

In substantially the same manner as in Working Example 6, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate gave colorless needles, m.p. 157-158°C.

Working Example 112

In substantially the same manner as in Working Example 15, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-(2-naphthyl)ethenyl]oxazole to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[2-[(E)-2-phenylethenyl]oxazolylmethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 117-118°C.

Working Example 113

In substantially the same manner as in Working Example 6, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-(2-naphthyl)oxazole to give 5-[2-[4-methoxy-3-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione. Recrystallization from ethyl acetate gave colorless crystals, m.p. 161-162°C.

Working Example 114

A mixture of 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione (435 mg), 4-(2-chloroethyl)morpholine hydrochloride (373 mg), potassium carbonate (277 mg), sodium iodide (150 mg) and N,N-dimethylformamide (DMF) (10 ml) was stirred for 14 hours at 80°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was then distilled off, and the residue was subjected to a silica gel column chromatography. From the fraction eluted with ethyl acetate - hexane (1:1, v/v), 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-morpholinoethyl)-2,4-oxazolidinedione was obtained as an oily substance. This oily substance was led to hydrochloride by substantially the same procedure as in Working Example

91.

Elemental Analysis for $C_{30}H_{33}N_3O_7 \cdot HCl \cdot 1/2H_2O$:

Calcd.: C, 60.76; H, 5.95; N, 7.09

Found : C, 60.83; H, 6.00; N, 7.03

Working Example 115

In substantially the same manner as in Working Example 114, 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(2-chloroethyl)piperidine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 91.

Elemental Analysis for $C_{31}H_{35}N_3O_6 \cdot HCl \cdot 3/4H_2O$:

Calcd.: C, 62.51; H, 6.35; N, 7.06

Found : C, 62.50; H, 6.25; N, 7.24

Working Example 116

In substantially the same manner as in Working Example 114, 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 91.

Elemental Analysis for $C_{37}H_{39}N_4O_6 \cdot HCl$:

Calcd.: C, 62.80; H, 5.70; N, 7.92

Found : C, 62.87; H, 5.71; N, 8.00

Working Example 117

In substantially the same manner as in Working Example 89, 5-[2-[4-methoxy-3-[2-(E)-2-phenylethenyl]-

4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with methyl iodide to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-methyl-2,4-oxazolidinedione as colorless crystals, m.p. 140-141°C.

Working Example 118

In substantially the same manner as in Working Example 107, 5-[2-[4-methoxy-3-[2-(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-chloro-3-iodopropane to give 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione as colorless needles, m.p. 107-108°C.

Working Example 119

To a mixture of 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione (0.256 g), potassium carbonate (0.069 g), sodium iodide (0.075 g) and N,N-dimethylformamide (DMF) (5 ml) was added 1-methylpiperazine (0.076 g). The mixture was stirred for 12 hours at 80°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off, and the residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with chloroform-ethanol (19:1, v/v), 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-methylpiperazin-1-yl]propyl]-2,4-oxazolidinedione was obtained as an oily product. This oily product was processed, by substantially the same procedure as in Working Example 91, with HCl-ethanol (10%) to give the corresponding dihydrochloride (0.186 g, 58%).

Elemental Analysis for $C_{32}H_{38}N_4O_6 \cdot 2HCl \cdot H_2O$:

Calcd.: C, 57.74; H, 6.36; N, 8.42

Found : C, 57.98; H, 6.06; N, 8.39

Working Example 120

In substantially the same manner as in Working Example 47, ethyl 6-(3-benzyloxy-4-methoxyphenyl)-2-hydroxyhexanoate was allowed to react with potassium cyanate (KCNO) to give 5-[4-(3-benzyloxy-4-methoxyphenyl)butyl]-2,4-oxazolidinedione as an oily product.

NMR(δ ppm in $CDCl_3$): 1.41-2.02(6H,m), 2.52(2H,t,J=7.2Hz), 3.87(3H,s), 4.79(1H,dd,J=7.4&4.6Hz), 5.15(2H,s), 6.71(1H,dd,J=8.6&2.0Hz), 6.72(1H,d,J=2.0Hz), 6.82(1H,d,J=8.6Hz), 7.29-7.48(5H,m), 8.09(1H,br s).

Working Example 121

In substantially the same manner as in Working Example 4, 5-[4-(3-benzyloxy-4-methoxyphenyl)butyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[4-(3-hydroxy-4-methoxyphenyl)butyl]-2,4-oxazolidinedione, m.p. 90-91°C.

Elemental Analysis for $C_{14}H_{17}NO_5$:

Calcd.: C, 60.21; H, 6.14; N, 5.02

Found : C, 60.13; H, 6.21; N, 5.02

Working Example 122

In substantially the same manner as in Working Example 6, 5-(4-hydroxybenzyl)-2,4-thiazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 182-183°C.

Working Example 123

In substantially the same manner as in Working Example 79, 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-thiazolidinedione was allowed to react with 4-(2-chloroethyl)morpholine to

give 3-(2-morpholinoethyl)-5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 129-130°C.

Working Example 124

In substantially the same manner as in Working Example 79, 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl-2,4-thiazolidinedione was allowed to react with 4-(2-chloroethyl)piperidine to give 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-3-(2-piperidinoethyl)-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 125-127°C.

Working Example 125

In substantially the same manner as in Working Example 79, 5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-thiazolidinedione was allowed to react with N,N-dimethylaminoethyl chloride to give 3-(2-dimethylaminoethyl)-5-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]benzyl]-2,4-thiazolidinedione. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p. 89-90°C.

Working Example 126

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxy-3,5-dimethoxyphenyl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-(2-naphthyl)ethenyl]oxazole to give 5-[3-[3,5-dimethoxy-[4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystallization from chloroform-ethanol gave colorless prisms, m.p. 181-182°C.

Working Example 127

In substantially the same manner as in Working Example 79, 5-[3-[3,5-dimethoxy-[4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-(2-

chloroethyl)morpholine to give 5-[3-[3,5-dimethoxy-[4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-morpholinoethyl)-2,4-oxazolidinedione as an oily product. This oily product was processed with HCl-methanol (10%) to give the corresponding hydrochloride.

Elemental Analysis for $C_{36}H_{39}N_3O_8 \cdot HCl \cdot 1/2H_2O$:

Calcd.: C, 62.92; H, 6.01; N, 6.11

Found : C, 62.68; H, 6.30; N, 5.98

Working Example 128

In substantially the same manner as in Working Example 79, 5-[3-[3,5-dimethoxy-[4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 1-(2-chloroethyl)piperidine to give 5-[3-[3,5-dimethoxy-[4-[2-[(E)-2-(2-naphthyl)ethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione as an oily product. This oily product was processed with HCl-methanol (10%) to give the corresponding hydrochloride.

Elemental Analysis for $C_{37}H_{41}N_3O_7 \cdot HCl \cdot H_2O$:

Calcd.: C, 64.01; H, 6.39; N, 6.05

Found : C, 64.31; H, 6.47; N, 5.97

Working Example 129

In substantially the same manner as in Working Example 79, 5-[3-[3-methoxy-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 4-(2-chloroethyl)morpholine to give 5-[3-[3-methoxy-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-morpholinoethyl)-2,4-oxazolidinedione as an oily product. This oily product was processed with HCl-methanol (10%) to give the corresponding hydrochloride.

Elemental Analysis for $C_{31}H_{35}N_3O_7 \cdot HCl \cdot 1/2H_2O$:

Calcd.: C, 61.33; H, 6.14; N, 6.92

Found : C, 61.49; H, 6.34; N, 6.87

Working Example 130

In substantially the same manner as in Working Example 79, 5-[3-[3-methoxy-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 1-(2-chloroethyl)piperidine to give 5-[3-[3-methoxy-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-(2-piperidinoethyl)-2,4-oxazolidinedione as an oily product. This oily product was processed with HCl-methanol (10%) to give the corresponding hydrochloride.

Elemental Analysis for $C_{32}H_{37}N_3O_6 \cdot HCl \cdot H_2O$:

Calcd.: C, 62.58; H, 6.56; N, 6.84

Found : C, 62.29; H, 6.75; N, 6.87

Working Example 131

A mixture of ethyl 2-chloro-4-(4-isopropoxyphenyl)butyrate (1.4 g), thiourea (1.5 g), sodium acetate (1.61 g) and ethanol (30 ml) was stirred for 7 hours under reflux, which was poured into water. Resulting crystalline precipitate was collected by filtration, which was added to ethanol (30 ml) - 2N HCl (30 ml). The mixture was stirred for 16 hours under reflux, which was poured into water, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off to give 5-[2-(4-isopropoxyphenyl)ethyl]-2,4-thiazolidinedione (1.37 g, 100%) as an oily product.

NMR(δ ppm in $CDCl_3$): 1.32(6H,d,J=6Hz), 2.05-2.9(4H,m), 4.19(1H,dd,J=9.5&4.0Hz), 4.4-4.6(1H,m), 6.83(2H,d,J=8.5Hz), 7.08(2H,d,J=8.5Hz), 8.29(1H,br s).

Working Example 132

In substantially the same manner as in Working Example 5, 5-[2-(4-isopropoxyphenyl)ethyl]-2,4-thiazolidinedione was allowed to react with titanium tetrachloride to give 5-[2-(4-hydroxyphenyl)ethyl]-2,4-thiazolidinedione. Recrystallization from acetone -

isopropyl ether gave colorless prisms, m.p. 175-176°C.

Working Example 133

A mixture of 2-[3-(4-isopropoxyphenyl)propyl]-1,3-dioxolan (2.53 g), 2,4-thiazolidinedione (1.78 g), piperidine (0.86 g) and acetic acid (30 ml) was stirred for 3 hours under reflux, which was then concentrated under reduced pressure. The concentrate was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). Then, the solvent was distilled off, and the residual oily substance was subjected to a silica gel column chromatography. From the fraction eluted with chloroform - ethyl acetate (9:1, v/v), 5-[4-(4-isopropoxyphenyl)butylidene]-2,4-thiazolidinedione was obtained as an oily product. This oily product was subjected to catalytic reduction in substantially the same manner as in Working Example 4, to give 5-[4-(4-isopropoxyphenyl)butyl]]-2,4-thiazolidinedione. Recrystallization from ether-hexane gave colorless prisms, m.p. 72-73°C.

Working Example 134

In substantially the same manner as in Working Example 5, 5-[4-(4-isopropoxyphenyl)butyl]-2,4-thiazolidinedione was allowed to react with titanium tetrachloride to give 5-[4-(4-hydroxyphenyl)butyl]-2,4-thiazolidinedione. Recrystallization from dichloromethane - isopropyl ether gave colorless prisms, m.p. 125-126°C.

Working Example 135

In substantially the same manner as in Working Example 6, 5-[4-(3-hydroxy-4-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate gave colorless

needles, m.p. 159-160°C.

Working Example 136

In substantially the same manner as in Working Example 6, 5-[4-(3-ethoxy-4-hydroxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-(3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate gave colorless needles, m.p. 160-161°C.

Working Example 137

In substantially the same manner as in Working Example 15, 5-[4-(3-hydroxy-4-methoxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate gave colorless needles, m.p. 118-119°C.

Working Example 138

In substantially the same manner as in Working Example 15, 5-[4-(3-ethoxy-4-hydroxyphenyl)butyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[4-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate gave colorless needles, m.p. 113-114°C.

Working Example 139

In substantially the same manner as in Working Example 114, 5-[4-[4-methoxy-3-[2-(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine to give 3-[3-[4-(3-

chlorophenyl)piperazin-1-yl]propyl]-5-[4-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{39}H_{43}ClN_4O_6 \cdot HCl \cdot 0.5H_2O$

Calcd.: C, 62.90; H, 6.09; N, 7.52

Found : C, 62.84; H, 6.21; N, 7.40

Working Example 140

In substantially the same manner as in Working Example 107, 5-[4-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chloropropyl)-4-phenylpiperazine to give 5-[4-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione. Reacrystalization from ethyl acetate - ethanol gave crystals, m.p. 102-103°C.

Working Example 141

In substantially the same manner as in Working Example 114, 5-[4-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine to give 3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-5-[4-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{40}H_{45}ClN_4O_6 \cdot 2HCl$

Calcd.: C, 61.11; H, 6.03; N, 7.13

Found : C, 61.21; H, 5.91; N, 7.00

Working Example 142

In substantially the same manner as in Working Example 107, 5-[4-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chloropropyl)-4-phenylpiperazine to give 5-[4-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]butyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate - ethanol gave crystals, m.p. 92-93°C.

Working Example 143

In substantially the same manner as in Working Example 107, 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chloropropyl)-4-phenylpiperazine to give 5-[2-[3-ethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate - ethanol gave crystals, m.p. 112-114°C.

Working Example 144

In substantially the same manner as in Working Example 119, 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(4-fluorophenyl)piperazine to give 3-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{37}H_{39}FN_4O_6 \cdot HCl \cdot H_2O$:

Calcd.: C, 62.66; H, 5.97; N, 7.90

Found : C, 62.62; H, 6.04; N, 7.76

Working Example 145

In substantially the same manner as in Working

Example 119, 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(4-methoxyphenyl)piperazine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{38}H_{42}N_4O_7 \cdot 2HCl \cdot 0.25H_2O$:

Calcd.: C, 61.33; H, 6.03; N, 7.53

Found : C, 61.38; H, 5.97; N, 7.30

Working Example 146

In substantially the same manner as in Working Example 119, 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(2-pyridyl)piperazine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(2-pyridyl)piperazin-1-yl]propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{36}H_{39}N_5O_6 \cdot 3HCl \cdot 1.5H_2O$:

Calcd.: C, 55.85; H, 5.86; N, 9.05

Found : C, 55.95; H, 5.61; N, 9.01

Working Example 147

In substantially the same manner as in Working Example 119, 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-phenylpiperazine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in

Working Example 79.

Elemental Analysis for $C_{37}H_{40}N_4O_6 \cdot 2HCl$

Calcd.: C, 62.62; H, 5.97; N, 7.89

Found : C, 62.47; H, 6.12; N, 7.81

Working Example 148

In substantially the same manner as in Working Example 119, 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(2-pyrimidyl)piperazine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(2-pyrimidyl)piperazin-1-yl]propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{35}H_{38}N_6O_6 \cdot HCl \cdot 0.5H_2O$:

Calcd.: C, 61.44; H, 5.89; N, 12.28

Found : C, 61.43; H, 5.93; N, 12.24

Working Example 149

In substantially the same manner as in Working Example 119, 3-(3-chloropropyl)-5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 1-(4-trifluoromethylphenyl)piperazine to give 5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(4-trifluoromethylphenyl)piperazin-1-yl]propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{38}H_{39}F_3N_4O_6 \cdot 2HCl$

Calcd.: C, 58.69; H, 5.31; N, 7.20

Found : C, 59.00; H, 5.49; N, 7.25

Working Example 150

In substantially the same manner as in Working Example 6, 5-[3-(4-hydroxyphenyl)propyl]-2,4-

oxazolidinedione was allowed to react with 4-chloromethyl-2-(3,4-dihydro-2-naphthyl)oxazole to give 5-[3-[4-[2-(3,4-dihydro-2-naphthyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate gave colorless prisms, m.p. 180-181°C.

Working Example 151

In substantially the same manner as in Working Example 15, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine to give 5-[2-[3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propoxy]-4-methoxyphenyl]ethyl]-3-[3-[4-(3-chlorophenyl)piperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{38}H_{48}Cl_2N_5O_5 \cdot 4HCl \cdot 0.5H_2O$:

Calcd.: C, 51.83; H, 6.07; N, 7.95

Found : C, 51.62; H, 6.02; N, 7.83

Working Example 152

In substantially the same manner as in Working Example 10, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, which was subjected to a silica gel column chromatography. From the fraction eluted with ethanol-chloroform (1:49, v/v), 5-[2-[3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propoxy]-4-methoxyphenyl]ethyl]-2,4-oxazolidinedione was obtained as an oily product.

NMR(δ ppm in $CDCl_3$): 2.00-2.31(4H,m), 2.64-2.83(8H,m), 3.25(4H,t,J=5.0Hz), 3.82(3H,s), 4.09(2H,t,J=6.2Hz), 4.62(1H,dd,J=4.4&7.6Hz), 6.71-6.87(6H,m), 7.15(1H,t,J=8.2Hz), 7.20(1H,s).

From the following fraction, 3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-5-[2-(3-hydroxy-4-

methoxyphenyl)ethyl]-2,4-oxazolidinedione was obtained as an oily product.
NMR(δ ppm in $CDCl_3$): 1.84(2H,quint,J=7.0Hz), 2.00-2.33(2H,m), 2.43(2H,t,J=6.8Hz), 2.53(4H,t,J=5.0Hz), 2.67-2.76(2H,m), 3.15(4H,t,J=5.0Hz), 3.61(2H,t,J=7.0Hz), 3.82(3H,s), 4.69(1H,dd,J=4.4&8.4Hz), 6.62-6.85(6H,m), 7.15(1H,t,J=8.2Hz).

Working Example 153

In substantially the same manner as in Working Example 1, 5-[2-[3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propoxy]-4-methoxyphenyl]ethyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 5-[2-[3-[3-[4-(3-chlorophenyl)piperazin-1-yl)propoxy]-4-methoxyphenyl]ethyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{37}H_{39}ClN_4O_6 \cdot 2HCl \cdot 0.5H_2O$:

Calcd.: C, 59.01; H, 5.62; N, 7.44

Found : C, 59.30; H, 5.67; N, 7.16

Working Example 154

In substantially the same manner as in Working Example 1, 3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 4-[(E)-2-phenylethenyl]benzylchloride to give 3-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-5-[2-[4-methoxy-3-[4-[(E)-2-phenylethenyl]benzyloxy]phenyl]ethyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{40}H_{44}ClN_3O_5 \cdot 2HCl \cdot 0.75H_2O$:

Calcd.: C, 62.67; H, 5.98; N, 5.48

Found : C, 62.65; H, 6.11; N, 5.41

Working Example 155

In substantially the same manner as in Working Example 3, 4-benzyloxycinnamaldehyde was subjected to condensation with 1-methylhydantoin to give 5-(4-benzyloxycinnamylidene)-1-methylhydantoin, which was subjected to catalytic reduction in substantially the same manner as in Working Example 4 to give 5-[3-(4-hydroxyphenyl)propyl]-1-methylhydantoin. Recrystalization from N,N-dimethylformamide (DMF) - water gave colorless prisms, m.p. 179-180°C.

Working Example 156

In substantially the same manner as in Working Example 15, 5-[3-(4-hydroxyphenyl)propyl]-1-methylhydantoin was allowed to react with 4-chloromethyl-2-[(E)-2-phenylethenyl]oxazole to give 1-methyl-5-[3-[4-[2-[(E)-2-phenylethenyl]oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]oxazolylmethyl]hydantoin. Recrystalization from chloroform - hexane gave colorless prisms, m.p. 154-155°C.

Working Example 157

In substantially the same manner as in Working Example 107, 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chloropropyl)-4-phenylpipeazine to give 5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate - hexane gave colorless needles, m.p. 130-131°C.

Working Example 158

In substantially the same manner as in Working Example 107, 5-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]-2,4-oxazolidinedione was allowed to react with 1-(3-chloropropyl)-4-phenylpiperazine to give 5-[2-(3-

benzyloxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product.
NMR(δ ppm in $CDCl_3$): 1.85(2H,quint,J=7.0Hz), 1.95-2.26(2H,m), 2.44(2H,t,J=6.7Hz), 2.56(4H,t,J=4.9Hz), 2.65-2.76(2H,m), 3.16(4H,t,J=4.9Hz), 3.61(2H,t,J=7.0Hz), 3.85(3H,s), 4.55(1H,dd,J=4.4&8.2Hz), 5.41(2H,s), 6.71-6.93(6H,m), 7.22-7.45(7H,m).

Working Example 159

In substantially the same manner as in Working Example 4, 5-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was subjected to catalytic reduction to give 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product.
NMR(δ ppm in $CDCl_3$): 1.86(2H,quint,J=6.8Hz), 1.96-2.34(2H,m), 2.45(2H,t,J=6.8Hz), 2.56(4H,t,J=5.0Hz), 2.68-2.77(2H,m), 3.17(4H,t,J=5.0Hz), 3.63(2H,t,J=6.8Hz), 3.84(3H,s), 4.70(1H,dd,J=4.4&8.4Hz), 6.63-6.77(3H,m), 6.82-6.94(3H,m), 7.27(2H,t,J=8.0Hz).

Working Example 160

In substantially the same manner as in Working Example 1, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-5-methyl-2-(2-naphthyl)oxazole to give 5-[2-[4-methoxy-3-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{40}H_{42}N_4O_6 \cdot 2HCl$

Calcd.: C, 64.25; H, 5.93; N, 7.49

Found : C, 64.32; H, 5.92; N, 7.47

Working Example 161

In substantially the same manner as in Working Example 1, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was allowed to react with 2-(2-benzofuranyl)-4-chloromethyl-5-methyloxazole to give 5-[2-[4-methoxy-3-[2-(2-benzofuranyl)-5-methyl-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{38}H_{40}N_4O_7 \cdot 2HCl$

Calcd.: C, 61.87; H, 5.74; N, 7.60

Found : C, 61.60; H, 5.79; N, 7.52

Working Example 162

In substantially the same manner as in Working Example 1, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was allowed to react with 2-(2-benzothienyl)-4-chloromethyl-5-methyloxazole to give 5-[2-[4-methoxy-3-[2-(2-benzothienyl)-5-methyl-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{38}H_{40}N_4O_6S \cdot 2HCl$

Calcd.: C, 60.55; H, 5.62; N, 7.43

Found : C, 60.35; H, 5.85; N, 7.30

Working Example 163

In substantially the same manner as in Working Example 1, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was allowed to react with 4-chloromethyl-2-(3,4-dihydro-2-naphthyl)oxazole to give 5-[2-[3-[2-(3,4-

dihydro-2-naphthyl)-4-oxazolylmethoxy]-4-methoxyphenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{39}H_{42}N_4O_6 \cdot HCl \cdot 1.5H_2O$:

Calcd.: C, 64.50; H, 6.38; N, 7.71

Found : C, 64.83; H, 6.12; N, 7.74

Working Example 164

In substantially the same manner as in Working Example 1, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was allowed to react with 2-[3,5-bis(trifluoromethyl)phenyl]-4-chloromethyl-5-methyloxazole to give 5-[2-[3-[2-(3,5-bis(trifluoromethyl)phenyl]-5-methyl-4-oxazolylmethoxy]-4-methoxyphenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione as an oily product. This oily product was led to hydrochloride by substantially the same procedure as in Working Example 79.

Elemental Analysis for $C_{38}H_{38}F_6N_4O_6 \cdot HCl \cdot 1.0H_2O$:

Calcd.: C, 55.99; H, 5.07; N, 6.87

Found : C, 56.11; H, 5.04; N, 6.67

Working Example 165

In substantially the same manner as in Working Example 1, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione was allowed to react with 4-[(E)-phenylethenyl]benzylchloride to give 5-[2-[4-methoxy-3-[4-[(E)-2-phenylethenyl]benzyloxy]phenyl]ethyl]-3-[3-(4-phenylpiperazin-1-yl)propyl]-2,4-oxazolidinedione. Recrystalization from ethyl acetate gave colorless needles, m.p. 138-140°C.

Formulation Example 1 (dosage per tablet)

(1)	Compound of Working Example 36	10.0 mg
(2)	Lactose	60.0 mg
(3)	Corn starch	35.0 mg
(4)	Gelatin	3.0 mg
(5)	Magnesium stearate	2.0 mg

A mixture of 10.0 mg of the compound of Working Example 36, 60.0 mg of lactose and 35.0 mg of corn starch was granulated, by using 0.03 ml of a 10 weight % aqueous solution of gelatin (3.0 mg in terms of gelatin), through a sieve of 1 mm mesh. The granules were dried at 40 °C, which were again subjected to sieving. The resulting granules were mixed with 2.0 mg of magnesium stearate, which was compressed. Thus-obtained core tablets was sugar-coated with a suspension consisting of sucrose, titanium dioxide, talc and gum arabic, followed by polishing with bee wax.

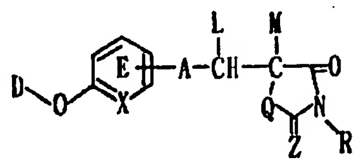
Formulation Example 2 (dosage per tablet)

(1)	Compound of Working Example 36	10.0 mg
(2)	Lactose	70.0 mg
(3)	Corn starch	50.0 mg
(4)	Soluble starch	7.0 mg
(5)	Magnesium stearate	3.0 mg

A mixture of 10.0 mg of the compound of Working Example 36 and 3.0 mg of magnesium stearate was granulated by using 0.07 ml of an aqueous solution of soluble starch (7.0 mg in terms of soluble starch) and dried, which was mixed with 70.0 mg of lactose and 50.0 mg of corn starch. The mixture was compressed to give a tablet.

CLAIMS

1. A heterocyclic compound represented by the formula:



wherein D stands for hydrogen atom or an optionally substituted hydrocarbon group;
X stands for CH or N;
A stands for a divalent aliphatic hydrocarbon group,
R stands for a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;
Z stands for oxygen atom or sulfur atom;
L and M independently stand for hydrogen atom, or they may optionally be combined with each other to form one bond; and
ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring;
or a salt thereof.

2. A compound or a salt thereof according to Claim 1, wherein the partial formula:

3. A compound or a salt thereof according to Claim 1, wherein D and R are respectively hydrocarbon groups substituted by an optionally substituted heterocyclic group.

4. A compound or a salt thereof according to Claim 1, wherein R is a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) an optionally esterified carboxyl group, (7) cyano group or (8) oxo group.

5. A compound or a salt thereof according to Claim 4, wherein the substituent in the optionally substituted heterocyclic group is C_{1-6} alkyl, C_{2-8} alkenyl, C_{3-8} cycloalkyl, C_{6-14} aryl, C_{7-14} aralkyl, C_{6-14} aryl-C_{2-6} alkenyl, an aromatic heterocyclic group, an aromatic heterocyclic-C_{1-6} alkyl group or an aromatic heterocyclic-C_{2-6} alkenyl group.

6. A compound or a salt thereof according to Claim 4, wherein the optionally substituted amino group is a C_{1-10} acylamino group, a mono- or di-C_{1-10} alkylamino group or a 4- to 6-membered cyclic amino group.

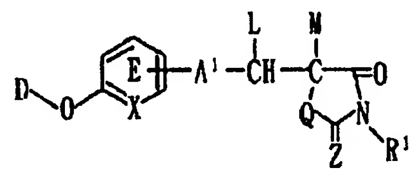
7. A compound or a salt thereof according to Claim 3, wherein the heterocyclic group is oxazolyl or thiazolyl.

8. A compound or a salt thereof according to claim 1, wherein X is CH.

9. A compound or a salt thereof according to claim 1, wherein A is a C_{1-7} divalent aliphatic hydrocarbon group.

10. A compound or a salt thereof according to claim 1, wherein Q and Z are oxygen atom.

11. A compound or a salt thereof according to claim 1, wherein L and M are hydrogen atom.
12. A compound or a salt thereof according to claim 1, wherein ring E may optionally have one to four substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halogen, amino, nitro and hydroxyl.
13. A compound or a salt thereof according to claim 1, which is
5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione;
5-[3-[3-methoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-thiazolylmethyl]-2,4-oxazolidinedione;
5-[3-[4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione;
5-[3-[3,5-dimethoxy-4-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]propyl]-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethyl]-2,4-oxazolidinedione;
5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-[4-(4-methoxyphenyl)piperadin-1-yl]propyl]-2,4-oxazolidinedione; or
5-[2-[4-methoxy-3-[2-[(E)-2-phenylethenyl]-4-oxazolylmethoxy]phenyl]ethyl]-3-[3-(4-phenylpiperadin-1-yl)propyl]-2,4-oxazolidinedione.
14. A pharmaceutical composition comprising a compound or a salt thereof as claimed in Claim 1.
15. An antitumor agent which comprises a compound represented by the formula:



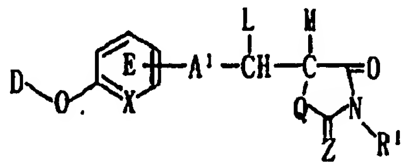
wherein D stands for hydrogen atom or an optionally substituted hydrocarbon group;
X stands for CH or N;
A^1 stands for a bond or a divalent aliphatic hydrocarbon group;
R^1 stands for hydrogen atom or a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;
Z stands for oxygen atom or sulfur atom;
L and M independently stand for hydrogen atom or they may optionally be combined with each other to form one bond; and
ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring; and when A^1 stands for a bond, D stands for an optionally substituted hydrocarbon group; or a salt thereof.

16. An antitumor agent according to claim 15, wherein A^1 is a C_{1-7} divalent aliphatic hydrocarbon group.

17. An antitumor agent according to claim 15, wherein R^1 is an optionally substituted hydrocarbon group.

18. An antitumor agent according to Claim 15, which is a therapeutic agent of breast cancer.

19. A tyrosine kinase inhibitor which comprises a compound represented by the formula:



wherein D stands for hydrogen atom or an optionally substituted hydrocarbon group;

X stands for CH or N;

A^1 stands for a bond or a divalent aliphatic hydrocarbon group;

R^1 stands for hydrogen atom or a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;

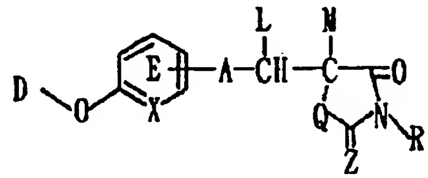
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;

Z stands for oxygen atom or sulfur atom;

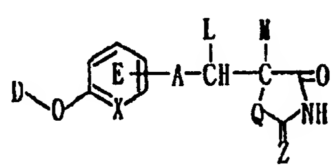
L and M independently stand for hydrogen atom or they may optionally be combined with each other to form one bond; and

ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring; and when A^1 stands for a bond, D stands for an optionally substituted hydrocarbon group; or a salt thereof.

20. A method of producing a compound represented by the formula:



wherein D stands for hydrogen atom or an optionally substituted hydrocarbon group;
X stands for CH or N;
A stands for a divalent aliphatic hydrocarbon group,
R stands for a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;
Z stands for oxygen atom or sulfur atom;
L and M independently stand for hydrogen atom, or they may optionally be combined with each other to form one bond; and
ring E may optionally be further substituted, and the substituent may optionally be combined with D to form a ring; or a salt thereof, which is characterized by allowing a compound represented by the formula:

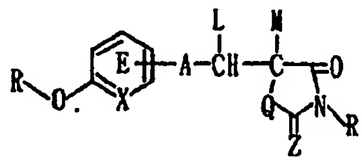


wherein each symbol is of the same meaning as defined above, or a salt thereof, to react with a compound

represented by the formula:

R-W wherein W stands for a leaving group and R is of the same meaning as defined above, or a salt thereof.

21. A method of producing a compound represented by the formula:



wherein

X stands for CH or N;

A stands for a divalent aliphatic hydrocarbon group,

R stands for a hydrocarbon group optionally substituted by (1) an optionally substituted heterocyclic group, (2) a halogen atom, (3) nitro group, (4) an optionally substituted amino group, (5) an optionally substituted acyl group, (6) a hydroxyl group optionally substituted by a hydrocarbon group or an acyl group, (7) a thiol group optionally substituted by a hydrocarbon group or an acyl group, (8) an optionally esterified carboxyl group, (9) cyano group or (10) oxo group;

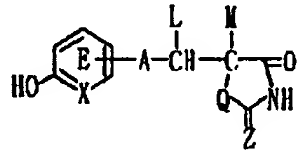
Q stands for $-N(R^0)-$ (R^0 stands for hydrogen atom or a lower alkyl group), oxygen atom or sulfur atom;

Z stands for oxygen atom or sulfur atom;

L and M independently stand for hydrogen atom, or they may optionally be combined with each other to form one bond; and

ring E may optionally be further substituted;

or a salt thereof, which is characterized by allowing compound represented by the formula:



wherein each symbol is of the same meaning as defined above, or a salt thereof, to react with a compound represented by the formula: R-W

wherein W stands for a leaving group and R is of the same meaning as defind above, or a salt thereof.

22. Method for treating cancer in a mammal in need thereof, which comprises administering such mammal a therapeutically effective amount of a compound as defined in claim 15 or a pharmaceutically acceptable salt thereof.

23. Method for treating diabetes in a mammal in need thereof, which comprises administering such mammal a therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable salt thereof.

24. Use of a compound as defined in claim 15 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating cancer.

25. Use of a compound as defined in claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating diabetes.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/01643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/44 C07D277/34 A61K31/425 A61K31/42 A61K31/415
C07D413/12 C07D417/14 C07D413/14 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 590 793 (SANKYO CO) 6 April 1994 cited in the application see claims	1-14,23, 25
Y	EP,A,0 612 743 (TAKEDA CHEMICAL INDUSTRIES LTD) 31 August 1994 cited in the application see claims	1-14,23, 25
A	EP,A,0 008 203 (TAKEDA CHEMICAL INDUSTRIES LTD) 20 February 1980 cited in the application see claims	1-25
A	EP,A,0 528 734 (ADIR ET COMPAGNIE) 24 February 1993 see claims	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 1996	01.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/01643

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 415 605 (BEECHAM GROUP PLC) 6 March 1991 see claims -----	1-25

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 96/01643

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 15 and 16 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

. ..ormation on patent family members

Interna   al Application No
PCT/JP 96/01643

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0590793	06-04-94	AU-B-	663611	12-10-95
		AU-A-	4496593	10-03-94
		CA-A-	2105149	01-03-94
		CN-A-	1090281	03-08-94
		CZ-A-	9301763	13-04-94
		FI-A-	933802	01-03-94
		HU-A-	67087	30-01-95
		JP-A-	6157522	03-06-94
		NO-A-	933080	01-03-94
		NZ-A-	248532	27-04-95
		US-A-	5436257	25-07-95
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		CN-A-	1098411	08-02-95
		HU-A-	70159	28-09-95
		JP-A-	7165735	27-06-95
		NO-A-	940610	29-08-94
		ZA-A-	9401321	25-08-95
		JP-A-	7101945	18-04-95
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		JP-A-	55022636	18-02-80
		JP-B-	62042903	10-09-87
		CA-A-	1131644	14-09-82
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		AU-B-	645709	20-01-94
		AU-A-	2110892	25-02-93
		CA-A-	2076444	21-02-93
		JP-A-	5213913	24-08-93
		JP-B-	7030055	05-04-95
		NZ-A-	244021	27-01-95
		US-A-	5330999	19-07-94
		US-A-	5296605	22-03-94

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interna' al Application No

PCT/JP 96/01643

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0528734		US-A- 5266582	30-11-93
		ZA-A- 9206276	02-03-93
EP-A-0415605	06-03-91	AU-A- 6128590	28-02-91
		CA-A- 2023905	26-02-91
		DE-D- 69006984	07-04-94
		DE-T- 69006984	09-06-94
		JP-A- 3090071	16-04-91
		US-A- 5132317	21-07-92

Form PCT/ISA/210 (patent family annex) (July 1992)